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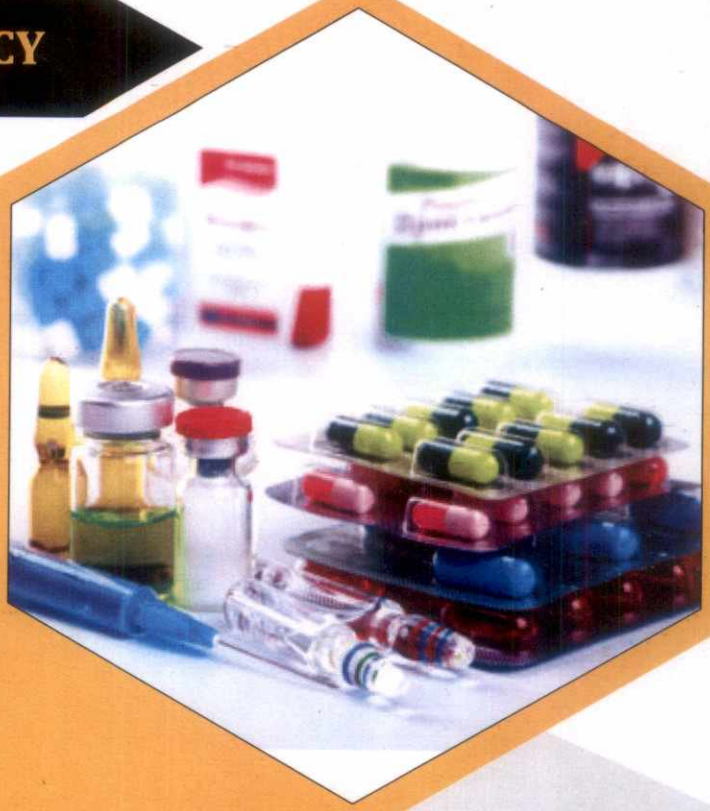

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PHARMACEUTICS

Dr. ASHOK HAJARE

NIRALI PRAKASHAN
ADVANCEMENT OF KNOWLEDGE

PHARMACEUTICS
Dr. ASHOK HAJARE

N6101

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Dedicated to ...

PROFESSION OF PHARMACY

'Thy Name is Healthcare'

A TEXT BOOK OF

PHARMACEUTICS

FIRST YEAR D. PHARM.
AS PER PCI EDUCATION REGULATIONS
(E.R. 2020)

Dr. ASHOK HAJARE
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Bharati Vidyapeeth College of Pharmacy, Kolhapur

Price ₹ 280.00

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Dedicated to ...

PROFESSION OF PHARMACY

'Thy Name is Healthcare'

Preface

I am very much delighted to handover the copy of first edition of Pharmaceutics book (Theory), strictly written according to new syllabus framed by Pharmacy Council of India (PCI), New Delhi as per Education Regulation 2020 (ER 2020) for Diploma Course in Pharmacy (D. Pharm.) under Regulation-7, to the First Year D. Pharm. students and faculty readers. This book is first of its kind available for this course in the pharmacy academia across India that fulfills the set objectives and covers all the contents prescribed in the syllabus for the course. Through this book I have grabbed an opportunity and made an attempt to provide the D. Pharm. students and faculty readers with the ready syllabus contents altogether to make it simple and understandable. The sequence of syllabus content is designed unit wise imparting better understanding of the subject matter. In this book wherever needed full forms and abbreviations, pictorial diagrams, tabular data, examples of formulations including marketed products and their manufacturers are given. This book has in all SEVEN Chapters; each begins with learning objectives for better understanding and ends with review questions for self evaluation. Each Chapter is covered in depth as per requirement taking into consideration the student's know how at entry level. Efforts have been taken to elaborate basic concepts of Pharmaceutics in most simple, lucid and technical language. If there are any corrections to any of the existing content in this book, readers are free to communicate to author and your efforts will be gratefully acknowledged.

I owe a great debt of gratitude to Hon. Dr. Vishwajeet Kadam, Secretary, Bharati Vidyapeeth Pune, for his encouragement. I am indeed very grateful to Prof. Dr. Shivajirao Kadam, Pro-Chancellor, Bharati Vidyapeeth University Pune for his consistent and cheerful support. I honestly extend my gratitude to Dr. H. N. More, Principal Bharati Vidyapeeth College of Pharmacy, Kolhapur for freedom to work and encouragement. My heartfelt thanks are due to Mrs. Suvarna and my Son Digvijay for their support, and to my parents mother Mrs. Sushila and father late Ananda Hajare for their blessings. I am truly grateful to Ms. Femi Babu for lending her voice in making audio commentary about the book and its contents.

I am very much thankful to Mr. Dineshbhai Furia, Mr. Jignesh Furia, Mrs. Roshan Khan, Mrs. Varsha Bodake, Mr. Ilyas Shaikh and Mr. Ravindra Walodare and Staff of Nirali Prakashan for bringing out nicely printed book.

Dr. Ashok Hajare
Author

Syllabus

1. • History of the profession of Pharmacy in India in relation to Pharmacy education, industry, pharmacy practice, and various professional associations.
   • Pharmacy as a career
   • Pharmacopoeia: Introduction to IP, BP, USP, NF and Extra Pharmacopoeia. Salient features of Indian Pharmacopoeia. **(7 Hours)**
2. **Packaging materials:** **(5 Hours)**
   Types, selection criteria, advantages and disadvantages of glass, plastic, metal, rubber as packaging materials.
3. **Pharmaceutical aids:** **(3 Hours)**
   Organoleptic (Colouring, flavouring, and sweetening) agents.
   Preservatives: Definition, types with examples and uses.
4. **Unit operations:** Definition, objectives/applications, principles, construction and workings of: **(9 Hours)**
   Size reduction: hammer mill and ball mill.
   Size separation: Classification powder according to IP, Cyclone separator, Sieves and standards of sieves.
   Mixing: Double cone blender, Turbine mixer, Triple roller mill and Silverson mixer homogenizer.
   Filtration: Theory of filtration, membrane filter and sintered glass filter
   Drying: working of fluidized bed dryer and process of freeze drying
   Extraction: Definition, Classification, method and applications
5. **Tablets** – coated and uncoated, various modified tablets (sustained release, extended-release, fast dissolving, double layered). **(8 Hours)**
   Capsules - hard and soft gelatine capsules. **(4 Hours)**
   Liquid oral preparations - solution, syrup, elixir, emulsion, suspension, dry powder for reconstitution **(6 Hours)**
   Topical preparations - ointments, creams, pastes, gels, liniments and lotions, suppositories and pessaries **(8 Hours)**
   Nasal preparations, Ear preparations. **(2 Hours)**
   Powders and granules - Insufflations, dusting powders, effervescent powders and effervescent granules. **(3 Hours)**
   Sterile formulations – Injectables, eye drops and eye ointments. **(6 Hours)**
   Immunological products: Sera, vaccines, toxoids and their manufacturing methods. **(4 Hours)**
6. **Basic structure, layout, sections and activities of pharmaceutical manufacturing plants Quality control and quality assurance:** **(5 Hours)**
   Definition and concepts of quality control & quality assurance, current good manufacturing practice (cGMP), Introduction to concept of calibration and validation.
7. **Novel Drug Delivery Systems** **(5 Hours)**
   Introduction, Classification with examples, advantages and challenges.

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Chapter ... 1

PHARMACY PROFESSION AND PHARMACOPOEIA

♦ **LEARNING OBJECTIVES** ♦

After completing the chapter, students will be able to:

- Recall the history of pharmacy and pharmacy practice, development of pharmacy profession and pharmaceutical industry in India.
- Get acquainted with the official pharmaceutical literature, its importance and scope.
- Know about historical development of pharmacy education in India.
- Know career opportunities in the field of pharmacy.
- Understand the history of profession of pharmacy.

1.1 INTRODUCTION

The history of pharmacy profession can be traced back to third millennium BC in Samaria. Samarian people, living in modern day Iraq, developed a cuneiform writing style on clay tablets which included lists of drugs of animal, vegetable and mineral origin that were used in the management of diseases, and prescriptions with details of the ingredients used in their compounding. Greeks were one of the first patrons of pharmacy profession. Earliest known records of preparation of medicines are Babylonian 2600 BC. The 'Ebers Papyrus' also known as 'Papyrus Ebers' is a continuous of some 60 feet long and foot wide written document dating back to 1550 BC. It includes 800 prescriptions (formulae), 700 drugs and describes prescriptions and modes of administration of drugs.

In China, the text 'Huangdi Neijing' listed the basic principles of pharmaceutical drug use in the third century BC. In India, Ayurvedic medicine was first described around 800 BC. Documents list the use of drugs together with charms for expelling demons. They make a reference to the God of medicine, 'Dhanvantari'. The 'Charaka Samhita' includes reference to drugs of animal, plant and mineral origin used until the first century AD. Hippocrates (460 BC) is considered to be the 'Father of Medicine'. He was associated with 'Hippocratic Corpus' dating to 420 – 370 BC, which lists 200 – 400 drugs of vegetable origin and describes the method of preparation.

What is Pharmacy?

❖ Pharmacy is the art and science of manufacturing and dispensing of drugs prepared from natural and synthetic sources and using them for the treatment and prevention of diseases.

King of Pontus (presently Turkey), Mithridates (134–63 BC) experimented with poisons and antidotes, tried them on himself and prisoners of war. Dioscorides (40-90 AD) a Greek physician and botanist, prepared the document 'De Materia Medica' around AD 60–78. Galen, a physician around AD 160, compiled medical knowledge and described the use of formulations made up of numerous plants which were referred to as 'Galenicals'. Profession of pharmacy started acquiring shape during 9th century in the civilized world around Baghdad. It slowly spread to Europe as alchemy and finally developed into chemistry.

Initially, the physician was a man of authority without formal education. When the physician could no longer cope with his work, he hired assistants to collect herbs for him and make preparations under his supervision. These assistants were called 'Pharmacopolae' but they were not 'Pharmacists'. The Arabs were of thought that those who prepare medicines could do so in an independent profession. Ultimately, this thought separated medicine and pharmacy and resulted in opening of first pharmacy shop in Bagdad in 770 under Caliph Al-Mansur. Pharmacists that time had much experience with medicines but did not possess the required education. During rule of Caliph Al Mamun (Bagdad) from 813 to 833 pharmacists started acquiring professional education.

Frederic II, a Roman emperor, in 1231 divided medicine into dogmatic medicine which makes diagnoses; manual medicine, which performs surgical interventions; and pharmaceutical medicine, which collects mixes and conserves medicines. The earliest recorded shop dealing with sales of medicines in London was opened in 1345. In England, Chaucer in his treatise 'The Knight's Tale' (written around 1386) used the word 'Pharmacy' to describe a medical preparation of plants "Farmacies of Herbs". 'Chemist and Druggist' was a term first used to describe both chemical and drug merchants and practitioners of the emerging profession of pharmacy from the late 1700s. The term 'Apothecary', was often used between the 1600s and 1800s, for individuals living in London who had passed the examinations of the 'Worshipful Society of Apothecaries of London', founded in 1617.

In America first hospital pharmacy began operations in 1752 with John Morgan as the first hospital pharmacist. 'Apothecaries Act' was passed in 1815 which stated that apothecaries will not have control over making medicines. Under this Act, apothecaries who passed specified course of 'Worshipful Society of Apothecaries' were licensed to conduct practice as general practitioners and called as 'Licentiate'. From 1815, the 'Society of Apothecaries' started assistants' examination and qualifying candidates were to compound and dispense drugs under the supervision of an apothecary, pharmacist or doctor.

The word 'pharmacist' was first used in a publication in England in 1834. By the time the new 'Pharmaceutical Society' adopted the term in the 1840s. Legislation in 1852 stated that the term 'Pharmaceutical Chemist' should only be used by people who had passed the Society's major examination or by certain unexamined members of the Pharmaceutical Society who owned their own businesses. A 'Register of Pharmaceutical Chemists' was compiled, but not published, from 1852 onwards. The term Pharmaceutical Chemist was retained after 1868, when registration became compulsory. Under the 'Pharmacy Act 1868' in England the term 'Chemist and Druggist' was used by the Pharmaceutical Society to denote those who had passed its minor examination, and those who met the minimum

requirement to register as a pharmacist. After 1868, the use of the title 'Chemist and Druggist' became legally restricted to registered pharmacists only. The terms 'Pharmacist' and 'Pharmaceutical Chemist' came later in the 1800s and was shortened to 'Chemist'. The 19th century witnessed various milestones being set in the field of pharmacy.

1.2 HISTORY OF PROFESSION OF PHARMACY IN INDIA

History of pharmacy profession in India can be divided in to three parts as ancient, pre-independence and post-independence history.

(a) Ancient Pharmacy Profession:

In mythological literature it is reported that Lord Brahma was the first teacher of Universe who wrote "Ayurveda" in 5000 BC. Sushruta, the son of Vishwamitra, did his work in the field of surgery. Ayurveda works on internal medicine whereas Sushruta-Samhita deals mainly with surgical medicine. Charaka and Sushruta were physicians as well as pharmacists who studied more than 1000 herbs. Ayurveda had been used by their devotees for medical purposes. It eventually spread over Asia with the advanced evolution of Buddhism. Vedic literature indicates that Lord Dhanvantari was worshiped as "God of Health". The reference to use of various herbs in treating diseases is mentioned in 'Rig-Veda" a text that contains the hymns for Soma and those for herbs. The concept of hospital was developed and practiced during rein of king "Ashoka the Great" in 226 BC. In Tamil Nadu during 900 AD, organized practice of hospital activity for the treatment of patients with diseases was discovered. In 1983, Portuguese practitioner Garcia de Orta reported use of Indian herbs in his treatise 'Cologuiousdos stroples a drogus da indica'. British traders brought the practice of allopathic system to India in 15th century. The Indian system of medicine declined during the Muslim rule while the Arabic or the Unani-Tibbi system flourished. The first general hospital was setup at Madras in 1664. Under British Rule Allopathic system got state patronage and become popular by the end of 19th century.

(b) Pre-independence Pharmacy Profession:

The first chemist shop was opened by Scotch Bathgate at Calcutta in 1811. In 19^{th} century, various activities related to pharmacy practice were performed according to London Pharmacopoeia. This situation forced back traditional practice of using medicines in India. The 'Bengal Dispensatory and Pharmacopoeia' was published in 1841 at Bishop's College Press Calcutta published by order of the then Government. In 1868, 'Pharmacopoeia of India' was published under editorship of Waring. The compilation of vernacular names of Indian medicinal plants and herbs was made by Mohideen Sheriff in 1869. The inception of pharmacy profession in India was marked in 1870 through conduct of examination for chemist and druggist. A formal training of the compounders was started in 1881 in Bengal. During 1901-1930 the systems of treatment for the prevalent diseases and ailment were Ayurvedic, Unani and Allopathy.

Research activities were started in Bombay (now Mumbai) as early as 1832 and the animal experiments for lymph started in Madras (now Chennai) in 1879, with initial success in 1880. The British government established small centers for production of small pox

vaccine and for plague at Haffkine Institute Mumbai in 1899 and King's Institute Madras in 1905. In India, first pharmaceutical company 'Bengal Chemical and Pharmaceutical Works' started in 1901 at Calcutta (now Kolkata) by Acharya Prafulla Chandra Ray. In 1903, a small pharmaceutical unit at Parel in Mumbai was started by Prof. T. K. Thakkar. Following the experience of setting up an industry he started second unit 'Alembic Chemical Works' at Baroda in Gujarat in 1907. Some of the British who owned pharmacies during independence include 'Spencer & Co.' at Madras, 'Madon & Co.' and 'Kemp & Co.' at Bombay and 'Whitehall Pharmacy' at Calcutta.

Drugs in India, all through this period, were mostly exported in crude form and imported in finished form. During World War-I (1914 – 1920) the imports of drugs was slowed down. There were no restrictions on the quality of drugs imported. The manufacturers abroad took advantage of the situation and dumped inferior quality medicines and adulterated drugs in India. In response to this situation and to control pharmacy practice in 1930, 'Dangerous Drug Act' was passed. Government of India (GOI) on 11th August 1930, appointed a Drug Enquiry Committee' (DEC) under the chairmanship of Late Col. R. N. Chopra to look into the problems of pharmacy profession in India and recommend the measures to be taken. The committee in its report, published in 1931, recommended many measures to avoid unethical practices. In 1940, British government bought 'Drug Bill' to regulate the import, manufacturing, sale and distribution of drugs in British India. This Bill was finally adopted as 'Drug and Cosmetics Act 1940' (D&C Act 1940). Up to 1940, all the allopathic drugs were imported from Europe but in later years some of these drugs began to be produced in India. In 1941, the first 'Drugs Technical Advisory Board' (DTAB) under this act was constituted. The first pharmacist post was created and filled at KEM hospital Mumbai. First 'All India Pharmaceutical Conference' (AIPC) was held at Banaras in January 1941 organized by Indian Pharmaceutical Association (IPA). Central Drugs Laboratory (CDL) in Calcutta was established under Directorship of Col. Chopra in 1947 with four scientific divisions.

(c) Post-independence Pharmacy Profession:

At independence in 1947, India inherited a system for the pharmacy profession from the British rulers that was unorganized and there were no legal restrictions on the practice of pharmacy. In 1948, the 'Pharmacy Act' was enacted as the nation's first minimum standard of educational qualification for pharmacy practice. Provisions of the Act are implemented through the 'Pharmacy Council of India' (PCI). The Act requires individual states to establish state pharmacy councils that are responsible for controlling and registering pharmacists in their respective states. English was the only language of instruction for all pharmacy institutions. Although slow initially, pharmacy education in India has undergone rapid and significant changes in the last couple of decades.

Today pharmaceutical industry in India is one of the largest and most advanced among the developing countries where pharmacists perform various tasks. Global pharmaceutical companies are establishing long term relationships with Indian pharmaceutical companies and the contract manufacturing affiliates in India, in addition to establishing manufacturing, research and development (R&D) and marketing bases. In India, there are several hundreds

of ayurvedic manufacturers, from small scale to very large companies. Now, the new generation pharmacists perform their functions in the fields of community, hospital, clinical research, regulatory, pharmaceutical bulk and finished product industries and in academics.

According to the Indian 'Retail Druggists and Chemists Association', in 1978, there were roughly 10,000 distributors and 125,000 retail pharmacies in India. Currently, there are over 8 lakh registered pharmacists involved in practice of pharmacy profession. Every year nearly 60000 pharmacy students are entering the profession amongst which diploma pharmacy people largely handle the pharmacy profession. State Pharmacy Council organizes various refresher training programmes for retail/hospital Pharmacists and to improve consumer awareness among the pharmacists to provide direct patient care. Since last three decades PCI, IPA and leaders in pharmacy profession have collectively undertaken initiatives to improve activities of this profession. Because of its wide scope and high demand people are attracted to pharmacy profession. Changeover of pharmacy profession from pharmacy practice to industry led to development of modern Indian pharmaceutical industry, which is now the 3rd in terms of volume and 14th in terms of value. The recent development in pharmacy profession is e-Pharmacy, the online sale of medicines. The e-pharmacy industry in India is still in its embryonic stages. Some of the well-known names in the market are Netmeds, EasyMedico and MedLife. The segment is dotted with startups such as 1mg, Practo, and Myra. Even traditional chemists such as Apollo Pharmacy have introduced their e-pharmacy segment.

1.2.1 Pharmacy Education in India

The first college in India was Madras Medical College established in 1835 where professional training was given to students for treating patients with drugs. In 1836, Calcutta Medical College was started at Kolkata. The first pharmacy college in Asia was started in Goa in 1842 by the Portuguese. The first two-year professional course 'Chemist and Druggist Diploma' was started in Madras Medical College in 1874. An industry oriented 3-year Bachelor of Pharmacy (B. Pharm.) program was started by Mahadeva Lal Schroff 'The Father of Pharmacy Education in India' at Banaras Hindu University Varanasi in 1932. Prof. Schroff started a separate branch of Pharmaceutical Sciences at Banaras Hindu University (BHU) Varanasi. The first M. Pharm. program was introduced in 1940 at BHU. In 1943 a committee appointed by Indian Government under the chairmanship of Sir Joseph Bhore recommended 3-tier system for pharmacy education. In 1944, B. Pharm. course was started at the Punjab University Lahore, which was oriented towards pharmacy practice which in later years oriented more towards industry. In 1945, 'Doctor of Philosophy' (Ph.D.) program was introduced at BHU. In 1947, GOI through Legislature brought the 'Pharmacy Bill' to regulate, control and standardize pharmacy education in India. In the same year, L. M. College of Pharmacy was established at Ahmadabad (Gujarat). Before India gained independence in 1947, there were only 3 institutes offering pharmacy degree programs.

Do you know!

- The first class of 'Chemists and Druggists' was conducted at Madras Medical College in 1870.
- It was a training programme to gain skills in the practice of pharmacy profession.

'Pharmacy Act' in 1948 provided minimum standard of educational qualification for pharmacy practice to regulate the practice, education, and profession of pharmacy. Provisions of the Act are implemented through the PCI and individual states established their state pharmacy councils. Initially pharmacy education was focused on training of professionals and compounding aspects of the drugs. Today, it includes a blend of theory and practical classes and examinations, besides including industrial or hospital/community training of varying periods depending on the program selected.

Pharmacy degree programs offered in India includes Bachelor of Pharmacy (B. Pharm.), Master of Pharmacy (M. Pharm.), Master of Science in Pharmacy [M.S. (Pharm.)], and Master of Technology in Pharmacy [M. Tech. (Pharm.)], Doctor of Pharmacy (Pharm. D.), and Doctor of Philosophy in Pharmacy (Ph.D.). The D. Pharm. program requires a minimum of 2 years of instructive coursework followed by 500 hours of required practical training anticipated to be completed within 3 months in either a hospital or community settings. Various activities recommended to be completed during this training period include stocking of drugs and medical devices; inventory control procedures; handling of prescriptions; dispensing and patient counseling. The B. Pharm. program involves 4 years of study in colleges affiliated with universities or in a university department. Through PCI Regulations 2014 the B. Pharm. and M. Pharm. curriculum was made uniform throughout the nation. At B. Pharm. the concept of practice school and a six month project is introduced. Students holding a B. Pharm. degree can earn an M. Pharm. degree in 2 years, of which the second year is devoted to research leading to a dissertation in pharmaceutics, pharmaceutical chemistry, pharmacology, and pharmacognosy. Recently, industrial pharmacy, pharmaceutical analysis, pharmaceutical quality assurance, pharmaceutical regulatory affairs, and pharmaceutical biotechnology have been introduced at M. Pharm. programs.

To train the graduate pharmacist to provide clinical-oriented services, the M. Pharm. program in pharmacy practice was introduced at JSS College of Pharmacy at Mysore (1996) and at Ooty (1997). Currently, Indian Government has set up 7 National Institutes of Pharmaceutical Education and Research (NIPERs) offering M.S. (Pharm.), M. Tech. (Pharm.), and higher-level degrees. Students with an M. Pharm. degree in any discipline can acquire a Ph. D. degree with an additional minimum 3 years of study and research. The Pharm. D. program which constitutes 6 years of full-time study was introduced in 2008 with the aim of producing pharmacists who had undergone extensive training at practice sites and could provide pharmaceutical care to patients. The Pharm. D. (post-baccalaureate, after B. Pharm.) program is a 3-year program.

Until early 1980s, there were 11 universities and 26 colleges offering pharmacy education at the bachelor's and master's levels. Since the late 1980s, rapid industrialization

of pharmaceutical sector, privatization, and economic growth, pharmacy education has been developed at much faster rate. Most of the institutions, however, are privately funded colleges or privately funded universities. In 2010, there were less than 900 pharmacy colleges in the country and since 2015 the pharmacy institutes have grown immensely accounting for around 2000 colleges in 2020.

Admission Eligibility Criteria: Admission to the first year of B. Pharm. program is made on the basis of marks obtained in the HSC examination in the science stream and scores at CET examinations. The eligibility to M. Pharm. program is based on academic performance at B. Pharm. or an entrance test (GPAT) or both. GAPT score qualifies a student to receive government scholarship during the period of their M. Pharm. study. B. Pharm. degree holders can join the Pharm. D. program at its fourth year.

Curriculum: Curriculum change for diploma and degree pharmacy programs is undertaken by central government notification through an amendment of the Pharmacy Act. It is framed through the education regulations of this Act. The present education regulation for D. Pharm. is ER 2020, for B. Pharm. and M. Pharm. it is ER 2014 and for Pharm. D. it is 2008. The curriculum for all the pharmacy programs is now same throughout the country.

Regulations: Pharmacy education in India is regulated by the PCI, under the Pharmacy Act of 1948, and the All India Council for Technical Education (AICTE), under AICTE Act of 1987. Pharmacist's registration is decentralized and the state pharmacy councils are responsible for registering pharmacists in their respective states. The PCI has no jurisdiction over M. Pharm. and other higher-level degree programs. The AICTE is primarily responsible for planning, formulating, and maintaining norms and standards in technical education, which include pharmacy. Pharmacy practice is governed by the D&C Act 1940, which stipulates the manufacturing, distribution, and sale of drugs. Currently, there is no regulatory body and regulatory control for clinical pharmacy practice. The AICTE is also responsible for quality assurance of pharmacy (D. Pharm., B. Pharm., M. Pharm.) programs through accreditation by National Board of Accreditation (NBA) constituted by the AICTE.

Pharmacy Programs in India...

- Diploma in Pharmacy, Bachelor of Pharmacy, Master of Pharmacy, Master of Science in Pharmacy, Master of Technology in Pharmacy, Doctor of Pharmacy, Doctor of Philosophy in Pharmacy and Integrated courses B. Pharm. + MBA or M. Pharm. + MBA.

1.2.2 Pharmaceutical Industry in India

Indigenous medicines were manufactured and used at small scale prior to the use of allopathic medicines during the British rule. The 'Bengal Chemical and Pharmaceutical Works' was the first indigenous industry established in 1892. About 13% of Indian drug product requirement was produced by several other indigenous firms during and after the World War II. Around 1930's efforts were also made in producing synthetic bulk drugs. The indigenous and foreign companies were involved mainly in manufacturing. During 1940's

and 1950's new medicines were marketed by multinational corporations (MNCs) but indigenous industry remained unaffected. A collaborative effort between Council of Scientific and Industrial Research (CSIR) and private manufacturing industry led to development, application and advancement of substantial skills in the pharmaceutical industry. However, post 1950 MNCs gained the position with new medicines being introduced in the Indian markets. A strong product patent system under the 'British Patents and Designs Act 1911' led to increasing influence of MNCs in the Indian pharmaceutical markets. As a result, by 1970s, the share of indigenous companies was reduced from 62% (1950) to 32% (1970).

During 1950's, the government established the Indian Drugs and Pharmaceuticals Limited (IDPL) and Hindustan Antibiotics Limited (HAL) with both indigenous and foreign technology collaboration. During late 1960s and in 1970s, there was an intentional attempt by government which made the way for growth of the domestic generic industry in India. Ayyangar report concluded that foreign patent holders dominated the industry through large number of patent filing and grants and patents law in force failed to work in national interest. As a result, Patents Act, 1970 was introduced that restricted patents only to process in case of pharmaceuticals and agricultural chemicals and the term of patents was reduced to 7 years. The Foreign Exchange Regulation Act, 1973 and the National Drug Policy, 1978 provided essential momentum to the growth of the Indian generic industry.

In late 1980 and early 1990, the Indian generic industry steadily increased the exports and became an important player globally. Substantial price controls in 1979 through the DPCO based on National Drug Policy 1978 led to entry of large number of firms in India. After 1990s, export led growth and increase in domestic consumption led to a dominating share of Indian firms in the market. In 1998, the domestic companies held 68% of the market share which grew to 77% in 2003 and 85% by 2020. Post 2005 the industry witnessed new trends with rapid developments that large and medium industries attempted to make strategies themselves. The generic industry had different bargain contributed by increased technical collaborations, merging and acquisitions.

Top FIVE Pharma Companies in India 2020:

- Sun Pharmaceutical Industries Ltd.: Founder – Dilip Shanghvi (1983)
- Dr. Reddy's Laboratories Ltd. : Founder – K. A Reddy (1984)
- Divi's Laboratories: Founder – Murali Divi (1990)
- Cipla: Founder – K. A. Hamied (1935)
- Aurobindo Pharma: Founder – P. V. R. Reddy and K. N. Reddy (1986)

The Indian pharma industry has grown from ₹ 237 crores (1980) to about 1.6 lakh crores (2020). The country is now ranked third in terms of volume of production and fourteenth largest by value. The share of export of drugs, pharmaceuticals and fine chemicals is more than ₹ 5000 billion. The domestic pharma industry has achieved historic milestones through world class cost effective drugs manufacturing of AIDS and Covid-19 medicines. Many

Indian companies are supplying life saving drugs to Africa, USA and Western Europe. In terms of scale, the Indian pharmaceutical market ranks among the top 10 in the world.

1.2.3 Pharmacy Practice in India

Pharmacy practice is the discipline of pharmacy which involves developing the professional roles of pharmacists. The scope of pharmacy practice includes more traditional roles such as compounding and dispensing of medications, and modern services related to health care, including clinical services, reviewing medications for safety and efficacy, and providing drug information. The origin of pharmacy practice in India can be traced back to British India when allopathic drugs were made available through drug stores in the 19th century. During the colonial period, the pharmacy profession was business oriented. Those who were trained to sell drugs were called drug sellers or dispensers. The pharmacy practice (community pharmacy) during pre-independence era was highly unregulated and there were no restrictions on the practice of pharmacy in India. The practice of prescribing and dispensing was normally a function performed by doctors. Most doctors trained their clinic assistants to dispense medicines and assist in the compounding of medicinal preparations. The functions and duties of assistants were ill defined and improperly understood.

The inception of pharmacy practice in India was marked by the 'Chemist and Druggist' program in 1870s to train students to gain skills in pharmacy practice. A formal training of the compounders was started in 1881 in Bengal. The B. Pharm. course at BHU was industry oriented while that at Punjab University was oriented towards pharmacy practice. Although the profession was oriented towards pharmacy practice at the introduction stage however as it grow, it became more industry oriented. Indian Systems of Medicines includes the systems originated in India and the systems originated outside but adapted in India, for example, Ayurveda, Unani, Siddha, Yoga, Naturopathy and Homeopathy. The profession of pharmacy practice has evolved through four stages.

Traditional Era: It was the period from early 20th century. The pharmacists were involved in the formulation, dispensing and study of medicinal properties of natural products of animal, plant, and mineral origins. In addition, they were involved in conducting animal experiments, systematic classification of drugs for treatment of disease and the process of obtaining extracts containing active principles from plants using techniques for preparing medications.

Scientific Era: It began after World War II. Application of scientific approach to medicine was begun during this period. Pharmaceutical industries were emerged and drugs were made by pharmacists in factories. They were involved in the scientific study of drugs and their mechanism of action including side effects and release characteristics of drug from dosage forms.

Clinical Era: This era began in second half of 20th century. During this period pharmacist were educated in the area of clinical pharmacy to establish pharmacokinetic parameters of a drug within the body over a period of time which includes absorption, distribution, metabolism, and elimination. In addition, much of the emphasis was given to pathophysiology to study disease and illnesses affecting the normal function of the body.

Industrialization Era: In India, the development of manufacturing pharmacy began in 20th century. It was followed by rapid mass production of medicines. Standardization, biologically prepared products, complex chemical synthesis, and increased use of parenteral medications were all part of this period. The pharmacists were the key players in the pharmaceutical industrial development in this era.

Pharmaceutical Care Era: Simultaneous to the industrialization era a pharmaceutical care philosophy was emerged that expanded the pharmacist's role to include appropriate medication use to achieve positive outcomes with prescribed drug therapy. Pharmacists are involved in monitoring response to therapy, educating patients and dispensing prescriptions. The beginning of this era concentrated on research to develop new drugs and medicines. These new medicines had a lot of adverse reactions of drugs so drug review and monitoring resulted wherein pharmacist are extending their services. Pharmacists now began to take a more hands on role in dispensing medications and patient education.

Today, pharmacists play an important role in healthcare sector as they take responsibility for patient's medicine related needs. In India, only the supply of medicines remains the core activity of the pharmacist. Most pharmacists in the country still hardly offer patient-oriented service. The role of the pharmacists in the industry and in community may change in the wake of the rapid growth of domestic medicine output and national healthcare expenditure.

1.2.4 Pharmaceutical Associations in India

There are number of pharmacy organizations and associations in India working for welfare of every individual within the purview.

1920: 'The Calcutta Chemist and Druggist Association' was formed which in 1926 changed their name as 'Bengal Chemists and Druggist Association'.

1923: The 'Pharmacist Association' was formed by chemist and druggist of Madras which was changed to 'Pharmaceutical Society of India' in 1925.

1935: Qualified professionals at BHU formed 'BHU Pharmaceutical Society'.

1935: United Provinces Pharmaceutical Association (UPPA)' was registered which became 'Indian Pharmaceutical Association' (IPA) in 1936.

1940: 'Allied Manufacturers and Distributors Association Ltd.' was formed in Mumbai.

1948: Indian Pharmaceutical Congress Association (IPCA) was formed at Calcutta. It is a federation of IPA, Indian Pharmacy Graduates' Association (IPGA), Indian Hospitals Pharmacist Association (IHPA), Association of Pharmaceutical Teachers of India (APTI) and All India Drugs Control Officers Confederation (AIDCOC) as its constituents.

1963: 'Indian Hospital Pharmacist Association' (IHPA) was formed at Delhi.

1965: 'Organization of Pharmaceutical Producers of India' (OPPI), a premier association of research and innovation driven pharmaceutical companies in India, was established at Mumbai. It caters to the needs of research based pharmaceutical industry to achieve the healthcare objectives of the nation.

1970: India joined 'Commonwealth Pharmaceutical Association' (CPA).

1973: 'Indian Pharmacy Graduates Association' (IPGA) was established at New Delhi.

1979: All pharmacy associations merged to form 'All India Organization of Chemist and Druggist' (AIOCD).

Some of the renowned and important associations and organizations are:

1. **Indian Pharmaceutical Association, Mumbai (1939):** An oldest association of pharmaceutical professionals in India, with over 13000 members actively involved in advising the government on matters of professional importance.
2. **All India Organization of Chemists and Druggists:** It has retail and wholesale pharmacist as its members has its offices at Taluka, District and State level with the name 'Chemist and Druggist Association'.
3. **Indian Drug Manufacturers Association, Mumbai (1961):** IDMA has over 1000 Indian large, medium and small industries and State Boards and was established to provide safe efficacious-affordable quality medicines..
4. **All India Cosmetics Manufacturers' Association (1964):** It is the only cosmetic association that promotes and protects the small scale cosmetic industry in India.
5. **Association of Pharmacy Teachers of India, Bengaluru (1966):** It is an association founded for creating better intercommunication and promotion of excellence in pharmacy education.
6. **Indian Hospital Pharmacists' Association, Pillani (1963):** IHPA is the national professional body of hospital pharmacists engaged in practice of pharmacy.
7. **Organisation of Pharmaceutical Producers of India (1965):** OPPI represents the research-based pharmaceutical companies in India.
8. **Bulk Drug Manufacturers Association, Hyderabad (1991):** It is an all India body of bulk drug manufacturers constituted to cater to the needs of the bulk drug industry.
9. **Association of Community Pharmacists of India:** It is an association of all persons engaged in, interested in or connected with community pharmacy.
10. **Indian Association of Colleges of Pharmacy:** IACP is a national organisation of its member colleges and their respective faculties.

1.3 PHARMACY AS A CAREER

Career in pharmacy is one of the best careers across the globe. Pharmacy is a part of healthcare services and today this discipline has made enormous progress in community, production and research. Dr. B. Suresh, the President of Pharmacy Council of India says 'Contrary to popular perception, increasing number of hospitals, nursing homes and pharmaceutical companies all over is a clear indication of the growing scope in pharmacy thus offering excellent and rewarding career opportunities both by way of jobs as well as in terms of starting own business'. The pharmacist has various job opportunities in

pharmaceutical industry, universities, teaching, hospitals, investigation and research institutes, Government departments, etc.

1. **As a Pharmacist:** The pharmacy diploma/degree holders can work in hospitals as hospital pharmacist, community pharmacist, consultant pharmacist or industrial pharmacist.
2. **Central and State Governments:** Pharmacists are employed within the central and state government departments such as Health Protection Branch of the Department of Health and Welfare, the Pest Control Division of Agriculture, the Department of National Defense, Provincial Research Councils, and the Provincial Departments of Agriculture or the Environment and Armed forces at various positions based on educational qualifications and experience. The Central and State Governments appoints Drugs Inspectors. Pharmacist has job opportunities in Government organizations such as CDRI Lucknow, NCL Pune, CSIR, IICT, RRL, AIIMS, CDSCO, and IMPCL. A Pharmacist has positions in FDA at state and central level. Pharmacist can even find jobs in railways, hospitals, navy and military, etc.
3. **Pharmaceutical Industry:** Some of the major positions in pharmaceutical industries where pharmacist is employed include production and manufacturing, research and development, quality control, quality assurance, pharmacovigilance, regulatory affairs, business operations, sales and administration, etc.
4. **Pharmaceutical Sales:** Registered pharmacists can sell bulk drugs as a bulk drug distributor or supplier and pharmaceutical products as distributor, wholesaler and retailer.
5. **Pharmaceutical Marketing:** The pharmaceutical industries for marketing of their products and services offer excellent opportunities for the pharmacy students, as they have a good knowledge about the drug molecules, their therapeutic effects, manufacturing and stability of drug products as well as drug-excipient and drug-drug interactions. The positions include Global Manager at higher level to Medical Representative at lower level.
6. **Academics:** Pharmacist degree holders are employed in the Universities and colleges of pharmacy in India. They are involved in teaching, research, public service, and patient care. D. Pharm. candidates are employed as laboratory assistant in the academic institutions.
7. **Higher Education:** There are many opportunities for D. Pharm. holder in higher education. A pharmacy student after D. Pharm. can opt for graduation and then post-graduation (M.Pharm. / M.S.) and Ph.D. Various certificate courses have been offered by government, public and private institutes. Pharmacy students can join a foreign language course and can immigrate to other countries easily. There are three degrees courses in pharmacy education available in developed countries namely; Pharm. D., M.S. and Ph. D.

8. **Pharmaceutical Journalism:** Pharmaceutical journalism is another opportunity for pharmacists which have great potential.
9. **Consultancy:** Pharmacists can offer his services as a consultant pharmacist for local, state, national, and international private and government organizations which include fields such as regulatory affairs, manufacturing, analytical services, documentation, approvals, research, marketing policies, etc.
10. **Clinical Research:** In clinical research organization (CRO) pharmacists are employed as Clinical Research Associate, Regulatory Affairs Associate, Clinical Data Manager, Clinical Development and Project Manager.
11. **Organizational Management:** Organizational management offers pharmacists on national and state associations and on boards of pharmacy. There is career for pharmacists in insurance sector too. They can work at managerial positions with health and welfare agencies.
12. **Opportunities Abroad:** There are lots of higher education and research opportunities in the developed countries. Pharmacists have placement opportunities in education, sales and manufacturing and in hospitals as councilor and as clinical pharmacist.
13. **Medical Transcription:** A pharmacist can work with physicians as medical transcriptor to maintain the patient treatment history, the drug to which patients are allergic etc.

Top FIVE Hospital Networks in India by Turnover...

- Dr. Lal Pathlabs Ltd.
- Narayana Hrudayalaya Ltd.
- Fortis Healthcare Ltd.
- Aster DM Healthcare Ltd.
- Apollo Hospitals Enterprise Ltd.

1.4 PHARMACOPOEIA

The word "Pharmacopoeia" is derived from the Greek words *'pharmakon'* meaning 'drug' and *'poieo'* means 'to make'. Pharmacopoeia is defined as a book prepared under the authority of the government of the respective countries that contains a list of medicinal substances, crude drugs and formulae for making preparations from them. Pharmacopoeia contain a list of drugs and other related substances regarding their sources, descriptions, standards, tests, formulae for preparations, action and uses, doses, storage conditions etc. It revised from time-to-time to introduce the latest information available as early as possible. In order to keep the size of book within reasonable limit certain less frequently used drug information and pharmaceutical excipients are omitted and in new editions certain new monographs are added, some are amended.

Pharmacopoeia is prepared by the expert amongst medical practitioners, teachers and pharmaceutical manufacturers. Pharmacopoeia is recognized as legal standards of purity, quality and strength by government agency of respective country of their origin. Pharmacopoeias prepared under the authority of the government of the respective countries, known as national pharmacopoeias, for example, IP, BP, USP, etc. The national pharmacopoeia is recognized as the reference book by the legislative authority (by law) of the respective country; whenever a conflict arises regarding drugs these books are referred to resolve the conflicts.

Importance of Pharmacopoeia:

(i) **Pharmaceutical industry:** In the invention of a new drug molecule huge amount of money is spent for the R&D. In such situations, drugs or products mentioned in the pharmacopoeias can be marketed without any further research on it because drugs listed in pharmacopoeia are tested safe and efficacious. Pharmacopoeia, being most authentic, provides various standards which should be met by the raw materials from which drugs and pharmaceuticals products prepared.

(ii) **Drug-administration:** The major objective of every industry is 'to make profit'. So doing this some industries ignore the quality aspects of the drugs and pharmaceuticals. As drugs are related to the health of human being and animals, this negligence is unjustifiable. Thus, every nation prepared their own drug related Acts, Laws and Rules. In the conflict situations between drug industries and the government, the first reference book that is conferred, regarding the quality of the product, is the pharmacopoeia.

(iii) **Academics:** The pharmacopoeias are reliable source of information regarding use of drugs and pharmaceuticals. The researchers always refer it at first hand during development of assay methods of certain drugs and testing the quality of a dosage forms. The information about microbiological and bioassays are given in details as appendices. Thus, usage of the drugs and raw materials, the adverse reaction, and many more information are provided in the pharmacopoeia.

1.4.1 Indian Pharmacopoeia (IP)

The historical developments of Pharmacopoeia in India traces back to 1563 and the credit go to Garcia da Orta a Portuguese physician-cum-teacher. The history of the IP began in the year 1833 when a committee of the East Indian Company's Dispensary recommended the Publication a Pharmacopoeia. The 'Bengal Pharmacopoeia and General Conspectus of Medicinal Plants' was written by W. B. O'Shaughnessy and published by Bishop's College Press Calcutta in 1844. This book listed the information about the most commonly used indigenous remedies. This was followed by IP 1868, written by Edward John Waring, which covered drugs of BP 1867 and indigenous drugs used in India. The supplement to IP 1868 was published in 1869 incorporating the vernacular names of indigenous drugs and plants. In 1885, the BP was made official book of standards in India. The colonial addendum of BP

1898 was published in 1900 which appeared as GOI edition in 1901. The Bengali and Hindi version of London Pharmacopoeia were made available in India from 1901 onwards.

The Bengali and Hindi version of London Pharmacopoeia were made available in India from 1901 onwards. After World War-I (1914 – 1920) there was complete absence of any restrictions on the quality of drugs imported, so manufacturers abroad took advantage of the situation. At that time few laws were there having indirect connection to drugs, but they were insufficient. In order to take over the control of this situation a Drug Enquiry Committee (DEC) was appointed in 1927 by the government who recommended the publication of an Indian National Pharmacopoeia. The GOI on 11th August 1930, appointed an 'Indian Pharmacopoeial Commission (IPC)' under the chairmanship of Late Col. R. N. Chopra to see into the issues of Pharmacy in India. This committee in 1931 reported that there was no recognized specialized profession of Pharmacy in India. In 1940, GOI brought 'Drugs Bill' to regulate the import, manufacturing, sale and distribution of drugs in British India. This Bill was adopted as D&C Act 1940. The first Drugs Technical Advisory Board (DTAB) under this Act was constituted in 1941.

In 1946, the Central Drugs Laboratory (CDL) was established at Calcutta. In 1944 GOI asked the DTAB to prepare the list of drugs used, in India, having sufficient medicinal value to justify their inclusion in pharmacopoeia. The work of preparing lists of drugs in use in India at those times which were not included in B.P. was given to late Col. R. N. Chopra along with other nine members, by Department of Health, Govt. of India. This work was published as an 'Indian Pharmacopoeial List (IPL)' in 1946 which formed the foundation for the true first official Indian Pharmacopoeia. After independence, the IPC was constituted, whose tenure was 5 years, under the chairmanship of late Dr. B. N. Ghosh in 1948 for publication of IP as its main function. This committee was assigned the task of preparing IP and to keep it up-to-date.

Remember! ...

- Indian Pharmacopoeia editions....

First: 1955	Second: 1955	Third: 1985	Fourth: 1996
Fifth: 2007	Sixth: 2010	Seventh: 2014	Eighth: 2018

First Edition: For the preparation of Pharmacopoeia of India, the pharmacopoeias of other countries, like British, Europe, United States, USSR, Japan, the National Formulary (USA) and Merck Index were consulted. The persons working in pharmaceutical industry, drug control laboratories, research and teaching institutions were also actively participated. The first edition of IP was published in 1955 by The Controller of Publications, Delhi, on the behalf of GOI, Ministry of Health and Family Welfare. Its cost was Rs. 5/- (Dollar 8). It was written in English and official titles of monographs were in Latin. It covered 986 monographs. This IP was published in fulfilment of requirements of D&C Act 1940 and Rules 1945 there under. The work of revision of the IP as well as compilation of new edition was taken-up simultaneously under the chairmanship of Dr. B. N. Ghosh, who died in 1958. After

Dr. B. N. Ghosh, Dr. B. Mukherjee, the Director of CDRI was appointed as the Chairman of IPC and the supplement of IP 1955 was published in 1960.

Second Edition: The second edition of IP was published in 1966 under Chairmanship of Dr. Nityanand. The official titles of monographs were in English. The doses were expressed in metric system. Usual strengths for tablets and injections were given. Formulations of the drugs were given immediately after the monograph of respective drugs. In all, 274 monographs from IP 1955 and their supplement were deleted and 93 new monographs were added. The supplement to this edition was published in 1975. In this supplement, 126 new monographs were included and 250 monographs were amended. Most importantly cholera vaccine was deleted.

Third Edition: In 1978, the IPC for third edition of IP was reconstituted by the GOI, under the Chairmanship of Dr. Nityanand, Director at CDRI, Lucknow. This edition of IP published in 1985 was presented in two volumes as Volume-I and Volume-II which included nine appendices. In all, a total of 261 new monographs were added and 450 monographs were deleted. Addendum I to IP 1985 was published in 1989 in which 46 new monographs were added and 126 were amended. Addendum II was published in 1991 wherein 62 new monographs were added and 110 were amended. In the IP 1985 and its Addendums, herbal drugs were included which had supporting definitive quality control standards.

Fourth Edition: The fourth edition of IP was published in 1996 and made effective from 1st December 1996. It was presented in two volumes. The Volume-I contains Legal Notices, Preface, Acknowledgments, Introduction, General Notices, and Monographs from A to O. The Volume-II contains Monographs from P to Z, Appendices, Contents of Appendices and Index. It covered 1149 monographs and 123 appendices. It included 294 new monographs and 110 monographs were deleted. Addendum I to IP 1996 was made effective from 31st December 2000 wherein 42 new monographs have been added. Addendum II was made effective from 30th June 2003 with 12 monographs on antiretroviral drugs and 7 monographs on formulations of these substances. A supplement to IP 4th edition was published in 2002 for Veterinary products which contained 208 monographs and 4 appendices. The Addendum to IP 4th edition was published in 2005 which included a large number of antiretroviral drugs and raw plants commonly used in making medicinal products not covered by any other pharmacopoeias.

Fifth Edition: The IPC for 5th edition was established in year 2005, which started working in existing CIPL with its Director as Member Secretary. The 5th edition of IP was published in 2007 and presented in user friendly format in 3 Volumes. Volume-I contained general notices and general chapters. Volume – II and III contained general monographs on drug substances, dosage forms and pharmaceutical aids. The General Notices, Monographs, New Testing Methods, etc., were based on the introduction of advanced technology and experimental methods widely adopted in India and abroad were added and updated. The contents of Appendices were revised by and large in consonance with those adopted internationally for monitoring the quality of the drugs. The monographs of special relevance to the common disease pattern of in India were given the special emphasis by incorporating

such medicines. The addendum to IP 2007 was published in 2008 that contained 72 new monographs. The GOI submerged the existing CIPL with IPC as a fully financed autonomous body from 1st January, 2009 located at NCR region in Ghaziabad. It had 3-tier structure that comprised of the general body of 25 members, governing body of 13 members and scientific body of 15-23 members from different related scientific fields.

Sixth Edition: The 6th edition of IP was published in 2010 by the IPC Ghaziabad through the untiring efforts of its members over a period of about two years. This edition was made effective from 1st September; 2010 and was presented in three volumes. The Volume-I contained the notices, preface, the structure of the IPC, Acknowledgements, Introduction, and the General Chapters, Volume II contained the General Notice, General Monographs on Dosage Forms and Monographs on Drug Substances, Dosage Forms and Pharmaceutical Aids (A to M), whereas, the Volume- III contained Monographs on Drug Substances, Dosage Forms and Pharmaceutical Aids (N to Z). This was followed by Monographs on Vaccines and Immune Sera for human use, herbs and herbal products, blood and blood-related products, biotechnology products and Veterinary products. Addendum to the IP 6th edition was published in 2012 which incorporated 52 new monographs.

Seventh Edition: The 7th edition of IP published in 2014 was presented in 4 volumes with DVD-ROM. IP 2014 was released by Gulam Nabi Azad, the then Health Minister at the Nirman Bhawan, New Delhi. This edition was published under chairmanship of P. K. Pradhan, Secretary, Health and Family Welfare, GOI. It was made effective from 1st January 2014. It incorporated 2548 monographs of drugs. A list of 577 new monographs not included in IP 6th edition and its addendum in 2012 was also added in this edition. First time 19 new radiopharmaceutical monographs are included in Pharmacopoeia. A separate volume of Veterinary products with 143 monographs along with 16 Appendices and a General chapter on Veterinary products is also introduced. IP Addendum 2015 to IP 2014 was released on 28th Nov. 2014 by Shri. Lov Verma the then Secretary and Chairman of Health and Family Welfare and of IPC, respectively. The IP Addendum 2016 to IP 2014 was released on 14th Nov. 2015 by Shri. J. P. Nadda, Minister of Health & Family Welfare, GOI. The total number of IP standards was almost 3000, at par with other International Pharmacopoeias.

Eighth Edition: The IP 2018, 8th edition, was released on 29th September, 2017 by C. K. Mishra, Secretary, Health and Family Welfare GOI. It was made effective from 1st January, 2018. This IP was brought out in 4 Volumes incorporating 220 new monographs (Chemical Monographs 170; Herbal Monographs 15; Blood and Blood related products 10; Vaccines and Immunosera for Human use monographs 02; Radiopharmaceutical monographs 03; Biotechnology Derived Therapeutic Products 06 and Veterinary monographs 14) and 366 revised monographs and 7 omissions. Addendum to IP 2018 was published in 2019.

1.4.2 British Pharmacopoeia

The regulation of medicinal products by officials in the United Kingdom (UK) dates back to the reign of King Henry VIII (1491–1547). The first book containing list of approved drugs with their preparations was published as 'London Pharmacopoeia' in 1618. The first edition

of the Edinburgh Pharmacopoeia was published by the Royal College of Physicians of Edinburgh in 1699. The first Dublin Pharmacopoeia was published in 1807. A Commission was first appointed by the General Medical Council (GMC) and the commissionerates were statutorily made responsible under the Medical Act 1858 for producing a 'British Pharmacopoeia' (BP) on a national basis.

In order to harmonize pharmaceutical standards London, Edinburgh and Dublin Pharmacopoeias were merged and the first edition of the BP was published in 1864. The BP is a comprehensive collection of quality standards for UK medicinal substances. It is an important statutory part in the control of drugs and medicines which complements and assists the licensing and inspection processes of the Medicines and Healthcare Products Regulatory Agency (MHRA) of the UK. The BP includes general notices, general monographs, and specific monographs providing mandatory standards for APIs, excipients, formulated preparations, herbal drugs, herbal drug products and herbal medicinal products, materials for use in the manufacture of homoeopathic preparations, blood-related products, immunological products, radio-pharmaceutical preparations, infrared reference spectra, appendices, supplementary chapters and comprehensive index. The BP (Veterinary) was published as a companion volume to the BP. It contained standards for substances and products used solely in the practice of Veterinary medicine in the UK.

The second edition of BP was published in 1867. The BP Commission was established in 1970 under Section 4 of the Medicines Act 1968. The 1874 Addendum to the BP 1867 was prepared by Attfield as the editor. The third edition was published in 1885 with Redwood, Attfield and Robert Bentley as joint editors. Another addendum was published in 1890, with Attfield again acting as its editor. The fourth edition of BP was prepared for the GMC Pharmacopoeia Committee with Nestor Tirard as its secretary, published in 1898. An Indian and Colonial Addendums were published in 1900, again with Attfield as its editor. In November 1903 the Council of the Pharmaceutical Society decided to produce its own reference book. The first edition of this reference book was published as British Pharmaceutical Codex (BPC) in 1907. The BP was supplemented by BPC that included information on drugs and other pharmaceutical substances not included in the BP, and provided standards for these. In November 1911, Tirard and Greenish were appointed as editors of the fifth edition, which was published in 1914. Drugs included for the first time included aspirin, diamorphine hydrochloride and phenolphthalein. Doses were given in both the imperial and metric systems. The sixth edition of BP became official in October 1932. There were seven Addenda to the BP 1932. A seventh edition of the BP was ready by November 1946, but it was not published until 1948 due to paper shortages. The eighth edition was published in 1953. In this edition titles of drugs and preparations were in English instead of Latin and metric system was used to denote measures. Ninth and tenth editions of the BP were published in 1958 and 1963, respectively. The tenth edition of BP contained almost 1000 monographs, 200 of which appeared for the first time. In 1963, the BP Commission proposed to create a common pharmacopoeia to serve the needs of a number of European countries which laid foundation of the European Pharmacopoeia (PhEur) in

1964. An eleventh edition of BP was published in 1968. The twelfth edition of BP was published in 1973 and the thirteenth edition in 1980. The fourteenth edition of BP was published in 1988 which contained two volumes with 2100 monographs. In 1993, fifteenth edition of BP was published. In 1998, a consolidated BP NF edition was published.

In BP 2007 monographs were introduced for materials specifically used in preparation of traditional Chinese medicines. In number of monographs the term 'prolonged release' was replaced with the term 'slow' and the term 'gastro-resistant' was replaced with 'enteric coated'. The BP 2008 contained approximately 3100 monographs for substances, preparations and articles used in practice. It was made effective from January 1, 2008. The next edition of BP was published in 2009. The BP from 2007 to 2009 was given in six volumes. The Volume-I and -II contained medicinal substances; Volume-III contained formulated preparations and products; Volume-IV contained supplementary chapters and Volume-V contained Veterinary while Volume-VI contained CD ROM version.

The BP 2010 was published by The Stationery Office (TSO), on the behalf of BP Secretariat, a part of the MHRA. The standards in the BP 2010 were made legally effective in the UK from 1st January 2010. The print edition of the BP 2010 comprises 4 volumes of the BP 2010 and a single volume of the BP (Veterinary) 2010. The BP 2012 was made legally effective from 1st January 2012. This edition of the BP comprises six volumes. The print edition of the BP 2012 comprises five volumes of the BP 2012 and a single volume of the BP (Veterinary) 2012. The BP 2013 includes six volume printed edition including the BP (Veterinary) 2013. This edition contained 41 new BP monographs, 40 new EP monographs, 619 amended monographs and, 6 new and 1 amended infrared reference spectra. The BP 2014 includes 3500 monographs. The BP 2014 comprises 5 volumes of the BP 2014 and a single volume of the BP (Veterinary) 2014, along with a fully searchable CD-ROM and online access to provide flexible resources. It was legally made effective from 1st January 2014. It includes 40 new BP monographs, 272 amended monographs, 3 new supplementary chapters, 4 new BP (Veterinary) monographs and 1 BP (Veterinary) supplementary chapter.

The Secretariat of BP Commission published BP 2016 and the BP (Vet) 2016. All items included in the 18th edition of the EuPhr together with those from Supplements 8.1 to 8.5, were incorporated in either of the BP 2016. The BP 2016 was published in August 2015. The BP 2016 includes almost 4,000 monographs and becomes legally effective on January 1, 2016. This edition sees the introduction of a download format for offline use and the new integrated website pharmacopoeia.com. The BP 2017 supersedes the BP 2016 and becomes legally effective on January 1, 2017. This edition incorporates new BP and PhEur monographs and a significant number of revised monographs. Also included is new information for unlicensed medicines and DNA barcoding. The BP 2018 supersedes the BP 2017 and becomes legally effective on January 1, 2018. This edition incorporates new BP and PhEur monographs and a significant number of revised monographs. It was available in six-volume printed edition, including the BP (Veterinary) 2018, single-user online licence and single-user download for offline use. BP 2019 was available from August 1, 2018 but made effective from January 1, 2019. BP 2020 is the most comprehensive collection of

authoritative official standards for UK pharmaceutical substances and medicinal products. It includes around 4,000 monographs including the BP (Veterinary) and all PhEur monographs, making the BP a convenient and fully comprehensive set of standards that can be used across Europe and beyond.

British Updates - Recent updates!

- New BP 2021 edition is legally made effective from 1st January, 2021.
- This edition has incorporated 30 new BP monographs and 20 new Ph. Eur. monographs along with a significant number of revised monographs.

Today BP is published on behalf of the Health Ministers of the UK, on the recommendation of the Commission on Human Medicines in accordance with Section 99(6) of the Medicines Act 1968 and notified in draft to the European Commission in accordance with Directive 98/34/EEC. It has been prepared by the BP Commission, with the collaboration and support of its expert advisory groups and panels of experts. Today, BP is used in more than 100 countries worldwide. BP, including the BP (Veterinary) and the PhEur are the two pharmacopoeias that have legal status within the UK. BP is published every year in August becomes effective on 1st January of the following year that incorporates all the monographs and texts of the PhEur.

1.4.3 United States Pharmacopoeia

The USP is for the United States of America published annually by the United States Pharmacopoeial Convention (USPC). It is published in a combined volume with the National Formulary as the USP-NF. Drugs subject to USP standards include both human and animal drugs. USP also sets standards for dietary supplements and food ingredients.

1800-1900: USP was founded in 1820 by 11 physicians in Washington DC. Dr. Spalding proposed a national pharmacopoeia in 1817. Jacob Bigelow was the primary author of the first Pharmacopoeia of the USA. The first USP contained 217 of the most fully established and best understood medicines in the USA. It was published by the authorities of the medical societies and colleges. In 1830 a seven member committee for revision of USP was created. The first revision of the USP was published in the same year and it was resolved to revise USP at 10-year intervals. Surgeons General of USA Army and Navy became first federal agencies to participate in USP revision. In 1848 'Drug Import Act' was passed and Federal legislation recognized the USP as an official compendium. In 1850, the colleges of pharmacy in USA were invited to participate in revision of the USP. The 1860 (USP IV) and 1870 (USP V) editions were published which included newer remedies and processes as well as technical methods. Charles Rice was elected as Chairman of the Committee of Revision in 1880 and soon initiated efforts to modernize USP monographs and methods. Clara Marshall appointed the first woman member of the USPC. The first NF 1888 was published by the American Pharmacists Association (APA). In 1880 and 1890, USP VI and USP VII editions were published, respectively.

1900-2000: USP VIII published in 1900 became official in 1905 with significant changes. Small pox vaccine was added to USP IX. The 4th edition of the NF was published in 1916. Revision cycle for USP was changed in 1942 and USP was published every 5 years. USP XII in 1942 was the first revision published under the 5-year schedule and it included monographs for injections for the first time, and compressed tablets finally were included although they were in use since Charles Rice's time. In 1949, USP Board appointed Lloyd Miller as Director of Revision. He was the USP's first salaried employee. The USP XIV and USP XV were published in 1950 and 1955, respectively. First United States Adopted Names (USAN) cumulative list was published in 1963. The USP XVII was published on September 1, 1965. William M. Heller in 1970 was appointed as Executive Director. In 1974 the NF was purchased by the USPC. In 1977, USP and NF scope was redefined with separation as USP specified standards for drug substances and dosage forms whereas NF specified standards for excipients. USP and NF were published under same cover in 1980 as USP Dispensing Information (USP DI). Jerome A. Halperin was appointed as USP executive Vice-President and Chief Executive Officer (CEO) at the 1990 USPC. In the convention, USP Members adopted a resolution to explore establishing standards for vitamins and minerals. In 1994, USP signed an agreement with the American Medical Association (AMA) to combine the information in AMA's Drug Evaluations database with the USP DI database to develop a single product that contains drug and therapeutic information. USP members adopted a resolution in 1995 to explore establishing standards for botanical dietary supplements. The USP23NF18 has ten supplements. The first supplement was published in January 1995 and last in May 1999. USP licensed USP DI and associated products in 1998 to Thomson Company and USP DI was published by their Micromedex subsidiary.

2000-2020: Roger L. Williams, M.D., became USP Executive Vice President and CEO at the USP Convention in April 2000. The Convention Members voted to change name of Committee of Revision to Council of Experts. The USP24-NF19 appeared from January 1, 2000. From 2002 USP–NF was published annually and from 2006 Spanish edition of USP was published. In 2007, USP–NF was published as a 3-volume set. Volume I contains General Chapters and Volume II and III contains Monographs. First supplement to USP30-NF25 appeared from August 2007 and second supplement from November 2007 which was considered official from May 2008. In 2009, USP published the USP Dietary Supplements Compendium and first Russian edition of USP–NF. The USP31-NF26 was a single-volume combination of USP and NF from 1st May, 2008. Monographs for drug substances and preparations are featured in the USP, with monographs for dietary supplements and ingredients appeared as a separate section of the USP. Excipient monographs are included in the NF. The USP32-NF27 published in 2009 contained more than 4,200 monographs and over 200 General Chapters. The USP33-NF28 published on October 1, 2010 which contained more than 4,400 monographs and over 200 General Chapters. The USP34-NF29 published in 2011 featured more than 4,500 monographs for drug substances, dosage forms, excipients, biologics, dietary supplements, and other therapeutics. USP34-NF29 offered more than 230 General Chapters. The USP35-NF30 was published and made official from May 1, 2012

to 30 April, 2013. The USP36-NF31 was published in November 2012. The USP37-NF32 was published in November 2014, USP38-NF33 in November 2015, USP39-NF34 in February 2016, USP40-NF35 on May 1, 2017, USP41–NF36 on November 1, 2017 and USP42–NF37 on November 1, 2018. The USP43–NF38 published in 2019 was the last edition available in print or on a USB flash drive. This current USP–NF includes more than 5,000 monographs for finished drug products (both chemical and biologic), as well as APIs and excipients. Specifically, the USP–NF includes more than 1,500 API monographs covering 50 therapeutic classes including oncology, cardiovascular, endocrine, infectious disease and mental health drugs. Starting with the First Supplement to USP 43–NF 38 that was published on February 1, 2020, is now available in the online format that contains all current USP–NF content.

Do you know!

- Recently USP has announced the release of six new Reference standards to support manufacturers and regulators in analyzing and monitoring potentially harmful nitrosamine impurities in the drug supply chain.

1.4.4 National Formulary (NF)

The National Formulary of India (NFI) is essentially meant for the guidance to the medical students, nurses and pharmacists working in hospitals and in sales establishments. In the preparation of NFI, the expert opinion of medical practitioners, teachers in medicine, nurses, pharmacists and pharmaceutical manufacturers was obtained. The selection of drugs for inclusion in the NFI was made by taking into consideration the relative advantages and disadvantages of the various drugs used; the extent of their use in current medical practice; and their availability in the country. Thus, NFI represents a broad consensus of medical opinion in respect of drugs and their formulations and provides the physician with carefully selected therapeutic agents of proved effectiveness which form the basis of national drug therapy.

In 1960, first edition of NFI was published by GOI, Ministry of Health and in 1966 second edition was published followed by third edition in 1979. It contains information about drug interaction, resistance, cumulative effects, drug dependence, prescription writing, etc. To address the need of publication of an updated version of NFI, Ministry of Health and Family Welfare, GOI on May 8, 2008 assigned this mandatory responsibility to the IPC, Ghaziabad and hence the NFI was published by the IPC on behalf of the GOI, Ministry of Health and Family Welfare. This NFI has been adopted from the WHO Model Formulary and thoroughly updated for its content, especially keeping in view the end user in India. After more than three decades the fourth edition was published in 2011 that included large number of additions and consequent deletions. To publish the 5th edition of NFI 2016, a High Power Committee was constituted by the Ministry of Health & Family Welfare, GOI on 23 Jul 2012, to identify the experts. The NFI 5th edition was published in 2016 to promote the rational use of medicines in the India and is priced at Rs. 630.

The formulations included in the NFI and the ingredients thereof should conform to the standards laid down in the current edition of the IP. If no standards are specified in the current edition but are specified in the immediately preceding edition of the IP then these standards would apply. In respect of drugs for which no standards have been laid down in the IP, these would have to conform to the standards laid down in the official pharmacopoeia of any other country wherein they are included. The provisions of the D&C Act 1940 and the Rules 1945 made there under including those relating to labeling and conditions of storage should also be observed.

1.4.5 Extra Pharmacopoeia

Extra Pharmacopoeia book's full title was "The Extra Pharmacopoeia of Unofficial Drugs and Chemical and Pharmaceutical Preparations" written by William Martindale. Martindale aimed to cover drugs and related substances reported for clinical interest anywhere in the world. It provided a useful source of information for patients arriving from abroad to identify their existing medication. This may reveal that a currently taken proprietary preparation is available under another brand name. Alternatively, if the drug is not available, the class of agent can be determined allowing a pharmacist or doctor to determine which alternative equivalent drugs can be substituted. Extra Pharmacopoeia was first published in 1883 under the title 'Martindale: The Extra Pharmacopoeia'. Martindale contains information on drugs in clinical use worldwide, as well as selected investigational and veterinary drugs, herbal and complementary medicines, pharmaceutical excipients, radiopharmaceuticals, vitamins and nutritional agents, vaccines, contrast media and diagnostic agents, medicinal gases, drugs of abuse and recreational drugs, toxic substances, disinfectants, and pesticides. 'Martindale: The Complete Drug Reference' is a reference book published by Pharmaceutical Press listing some 6000 drugs and medicines used throughout the world, including details of over 180000 proprietary preparations. It also includes almost 700 disease treatment reviews.

Martindale book is arranged into two main parts followed by three extensive indexes. First part is 'Monographs on drugs and ancillary substances' listing over 6,000 monographs arranged in 49 chapters based on clinical use with the corresponding disease treatment reviews. Monographs summarize the nomenclature, properties, and actions of each substance. A chapter on supplementary drugs and other substances covers 1190 monographs on new drugs, those not easily classified, herbals, and drugs no longer clinically used but still of interest. Monographs of some toxic substances are also included. The second part is preparations that include over 180000 items from 43 countries and regions, including China. This book has three indexes namely; Directory of Manufacturers, Pharmaceutical Terms in various languages and General Index. The Directory of Manufacturers has list of some 20000 entries. Pharmaceutical terms in various languages index lists nearly 5600 pharmaceutical terms and routes of administration in 13 major European languages as an aid to the non-native speaker in interpreting packaging, product

information, or prescriptions written in another language. The General Index is prepared from 175000 entries which include approved names, synonyms and chemical names; a separate Cyrillic section lists non-proprietary and proprietary names in Russian and Ukrainian language. The digital versions of Extra Pharmacopoeia include an additional 1000 drug monographs, 60000 preparation names, and 5000 manufacturers. To date there have been 38 editions of 'Martindale: The Complete Drug Reference'. The 38th edition was published in June 2014 by the London Pharmaceutical Press.

1.5 SALIENT FEATURES OF INDIAN PHARMACOPOEIA

The term salient feature is defining elements that distinguish one target from another. Following are some important distinguishing features of each edition of IP:

First Edition:

(1) The titles of monographs have been given in Latin language. Abbreviated titles for use in prescription have been given immediately below the Latin title. The English title has also been given below the abbreviation title.

(2) The weights and measures have been given in metric system.

(3) All statements contained in the individual monographs have been considered as constitute standards for the official substances.

(4) Doses are expressed both in the metric system as well as in the English system.

(5) A list of preparations has been given at the end of some of the monographs.

Second Edition:

(1) The titles of monographs have been changed from Latin to English and the words of the title, for example, 'Injection of Aminophylline' have been changed to 'Aminophylline Injection'.

(2) Doses are expressed in the metric system only.

(3) Solubility is expressed in parts of solvent per unit part of solute.

(4) The preparations of a drug have been given immediately after the monograph on the parent drug.

(5) The test for sterility has been modified to provide for detection of fungi in addition to aerobic and anaerobic bacteria.

Third Edition:

(1) The new analytical techniques such as Flame Photometry, Flurometry, Electrophoresis and Photometric Haemoglobinometry have been introduced.

(2) Dissolution test has been introduced in the case of certain tablets.

(3) Disintegration test has been amended by modifying the design of the apparatus and method of testing.

(4) A microbial limit test has been prescribed for certain pharmaceutical aids and oral liquid preparations.

(5) The pyrogen test has been revised to make the test less time-consuming.

Fourth Edition:

(1) The text is available in two volumes.

(2) The computer-generated structural formulae have been introduced.

(3) Some titles have been changed to include the more commonly accepted names of India, for example, 'Hyoscine Hydrobromide' as 'Scopolamine Hydrobromide'.

(4) Infra-red and ultra-red absorption spectrophotometric tests for identification of drug substance have been introduced as alternative tests to the classical chemical tests.

(5) The infra-red reference spectra of a number of drugs have been given in appendix.

Fifth Edition:

(1) This edition is presented in three volumes.

(2) General chemical tests for identification have been almost eliminated and more specific infrared and ultraviolet spectrophotometric tests have been given.

(3) The test for pyrogens involving the use of animals has been eliminated and the test for bacterial endotoxins has been introduced.

(4) The test for abnormal toxicity is confined to certain vaccines.

(5) The use of chromatographic methods has been extended in assays to large number of pharmaceutical products.

Sixth Edition:

(1) The number of monographs of excipients, anticancer drugs, herbal products and antiretroviral drugs has been increased.

(2) Monographs of Vaccines and Immunosera are upgraded in view of development of latest technology in the field.

(3) A new chapter on Liposomal products and a monograph of Liposomal Amphotericin B injection is added.

(4) A chapter on NMR is incorporated in Appendices.

(5) The chapter on microbial contamination is updated to a great extent to harmonize with prevailing international requirements.

Seventh Edition:

(1) This edition includes advanced technology and experimental methods widely adopted in India and abroad.

(2) The standards are prescribed for drugs produced and/or marketed in India to contribute the control and assurance of the quality of the medicines.

(3) This edition is presented in four volumes.

(4) Drugs and their formulations not in use now-a-days are omitted.

(5) It incorporates 2548 monographs of drugs out of which 577 are new monographs consisting of APIs, excipients, dosage forms, antibiotic monographs, insulin products and herbal products etc.

Eighth Edition:

(1) The new edition of Indian Pharmacopoeia has been brought out in 4 Volumes.

(2) Standards for new drugs and drugs used under NHP are included.

(3) 53 New Fixed Dose Combinations (FDCs) monographs have been included, out of which 25 FDC monographs are not available in any Pharmacopoeia.

(4) More specific infrared, ultraviolet spectrophotometer and HPLC tests have been given emphasis.

(5) The use of chromatographic methods has been greatly extended to assess the nature and extent of impurities in ingredients and products.

REVIEW QUESTIONS

1. What is Pharmacy and Pharmacy profession?
2. What is Ebers Papyrus?
3. Which China text listed the basic principles of pharmaceutical drug use in the third century BC?
4. What is Charaka Samhita? Who is called as Father of Medicine?
5. What is Materia Medica and galenicals?
6. In ancient times when the physicians could no longer cope with their work what they did?
7. Which was the earliest recorded shop dealing with sales of medicines?
8. Who was the first hospital pharmacist in America?
9. When and by whom the word Pharmacy was used first time?
10. What was the 'Apothecaries Act' related to?
11. What is Register of Pharmaceutical Chemists?
12. Write about ancient history of pharmacy profession.
13. Discuss pre-independence history of pharmacy profession.

14. What are the post-independence major developments of pharmacy profession?
15. Discuss history of profession of pharmacy in India.
16. When and where the first pharmacist post was created and filled in India?
17. When, where and by whom the first 'All India Pharmaceutical Conference' was held in India?
18. Explain development of pharmacy profession.
19. Who is called Father of Pharmacy in India?
20. When and where first pharmacy course was started in India?
21. What was the recommendation of Sir Joseph Bhore Committee on pharmacy Education in India?
22. When and where B. Pharm., M. Pharm. and Ph. D. course in India were started?
23. Elaborate upon history of pharmaceutical education in India.
24. What are major outcomes of Pharmacy Act 1940?
25. What is difference between B. Pharm. and Pharm. D. programs?
26. Comment on regulation of pharmacy education in India.
27. Which was the first indigenous pharmaceutical company? When, where and by whom it was started?
28. Name pharmaceutical industries started by Indian Government in 1950.
29. What was conclusion of Ayyangar report examining the legislation?
30. What is current status of Pharmaceutical industry at global level?
31. Write about history and development of pharmacy practice in India.
32. Enlist various associations constituted in pharmacy profession.
33. Enlist and explain different career options available for pharmacy students.
34. Focus a light on career opportunities available to students after completion of D. Pharm. program.
35. What is Pharmacopoeia? What are its objectives?
36. What is major function of Indian Pharmacopoeia Commission?
37. Why Drug Enquiry Committee was constituted? What is its major role?
38. What are full forms of DTAB and CDL? What are their main functions?

39. What is importance of Pharmacopoeia?
40. Discuss history of Pharmacopoeia of India.
41. Name Chairman's of first, second and third edition of I.P.?
42. List out various editions of Indian Pharmacopoeia along with its one major change.
43. List out salient features of first edition of I.P.
44. Write about salient features of recent edition of I.P.
45. Write short notes on:
    (i) British Pharmacopoeia
    (ii) United State Pharmacopoeia
    (iii) National Formulary of India.
    (iv) The Extra Pharmacopoeia.

Chapter ...2

PACKAGING MATERIALS

♦ LEARNING OBJECTIVES ♦

After completing the chapter, students will be able to:

- Define packaging; know its significance and types.
- Have a good understanding of the various packaging materials used, their characteristics and how they are manufactured.
- Understand the risks involved in packing materials and operations and what the QP needs to be particularly aware of.
- Gain practical information on how to improve the control of packing materials.
- Ensure and understand the plethora of challenges associated with pharmaceutical packaging.

2.1 INTRODUCTION

Pharmaceutical package is an integral part of pharmaceutical product. It is defined as an article or device which contains the pharmaceutical product and the container may or may not be in direct contact with the product. The container which is designed for pharmaceutical purpose must be stable. Pharmaceutical packaging material plays a vital role in the stability of the pharmaceutical dosage form. Packaging should be such that it should maintain the integrity of the dosage form, should be inert in nature, should not be fragile, and should have good mechanical strength.

Packing is enclosing of an individual item, or several items, in a container, usually for shipment, delivery or storage done by hand and machine. Pharmaceutical packaging is a combination of components necessary to contain, preserve, protect and deliver a safe, efficacious drug product in such a way that at any time point before expiration date of the drug product, a safe and efficacious dosage form is available.

Packaging is a process in which the pharmaceuticals are suitably placed so that they retain therapeutic effectiveness of active ingredients actives till they are consumed. It is employed by means a collection of different packaging materials which encase the pharmaceutical product from initial manufacturing step to the end use by consumer. It is a multiple user providing presentation, protection and identification information about a product during storage, carriage and display until the product is consumed. The important

considerations for packaging include desire to improve efficacy of dosage form, cost of packaging material and compliance with the drug packaging regulations.

(a) Types of Packaging Materials:

Pharmaceutical packaging is most commonly used to store and protect drugs. Packaging of pharmaceuticals is essential for identification purposes, for marketing and promoting different brands, and for facilitating the use of pharmaceutical products. In addition, it can be used for barrier protection, agglomeration of small doses, and transmission of information, security, convenience, and portion control. There are several different types of packaging materials used for pharmaceutical products.

(b) Classification of packaging Materials:

1. **Glass:** Type I, II, III and IV glass, colored glass.
2. **Metals:** Aluminium, tin, lead, etc.
3. **Rubbers:** Natural rubber, neoprene rubber, nitrile rubber, butyl rubber, chlorobutyl rubber, bromobutyl rubber, silicone rubber, etc.
4. **Plastics:** Polyethylene, polystyrene, polycarbonate, polyvinyl chloride, polyvinylidene chloride, polychlorotrifluoro ethylene, cyclic olefin copolymers, polypropylene, etc.
5. **Fibrous materials:** Cotton, paper and jute.
6. **Films, Foils and laminates:** Regenerated cellulose, cellulose coatings, foil and paper.

(c) Types of Packages:

1. **Primary package:** The primary packaging consists of those packaging components and subcomponents which have a direct contact with the pharmaceutical formulation such as bottle, cap, cap liner, label, etc. The main functions of the primary package are to contain and to restrict any chemical, climatic or biological or occasionally mechanical hazards that may cause or lead to product deterioration.

   Examples: Aerosol cans, glass and plastic bottles, plastic bags, wrappers, blister and strip packs, envelopes, cushioning, etc.

2. **Secondary package:** The packaging external to the primary package is known as the secondary packaging. This package provides additional physical protection necessary during safe warehousing and for refill packaging. This packaging is to carry information about drug product.

   Examples: Boxes, leaflets, cartoons, shrink-wraps, corrugated shippers, pallets, etc.

3. **Tertiary package:** Tertiary packaging facilitates the protection, handling warehousing, storage and transportation of a series of sales units or secondary packaging in order to group everything into unit loads during transit. It is used to protect not only the products for shipping in the distribution process or storing but also its secondary and primary packaging. This type of packaging is rarely seen by the consumer.

Examples: Barrels, brown cardboard boxes containers, slip sheets, crates, edge protectors, wood pallets, shrink and stretch wraps.

(d) Components of Packaging:

1. **Container:** Container is a part of package in which the formulation is placed and enclosed that remains in direct contact with the drug.
2. **Closure:** Closure is a part of some packagings that tightly packs the container to exclude oxygen, carbon dioxide, moisture, and microorganisms and prevent the loss of water and other volatile substances from the product.
3. **Carton/outer:** Carton is the outer covering of package, which provides secondary protection against mechanical and other environmental hazards which also serves to display of written information. The cartons are made up of cardboard, molded wood pulp and expanded polystyrene.
4. **Box:** It is used to pack multiples of products. The box provides primary defense against external hazards and have shock absorbing features. The boxes are made up of thick cardboard and wood.

Table 2.1: Pharmaceutical packaging materials and its uses

Type	Uses
Glass	Bottles, vials, ampoules, syringes, cartridges, parentral containers, aerosol container.
Plastic	Bottles, syringes, parentral containers, tubes, bags, laminate, pouches, lids, tapes, aerosol, container (dip tube, gasket housing button, stems).
Metals	Collapsible tubes, foils, needles, aerosol container, cans.
Rubber	Closures, vial wrappers, caps, plungers.
Paper/cardboard	Labels, inserts, display units, pouches, laminates, cartons, boxes, foils, gum tapes, paper drums.

(e) Advantages of Packaging:

1. Packaging helps to maintain stability of the product.
2. It protects the product from physical impacts such as hitting, wetting, and bruising.
3. It helps for the product to reach the consumer in economic way with ease of storage.
4. It provides with ease of choice and usage with the information it holds.
5. The package with details written on label provides convenience to the consumer.
6. Decreases product costs by packaging in small quantities.
7. Packaging provides hygiene.

2.2 SELECTION CRITERIA FOR PACKAGING MATERIALS

The pharmaceutical packaging materials contain important features and functions such as protection against all adverse external influence that can alter the properties of the product, Packaging provide protection against microbial contamination and physical damage. Packaging is used to carry the correct information and identification of the product. It can be used to serve multiple functions such as temper evident, child resistance and anti-counterfeiting. Selection of appropriate packaging prevents any wastage such as leakage or deterioration that may occur during transportation, distribution and handling. Usually good packaging extended the shelf lives of the products. A lucrative packaging and presentation encourages consumers to buy products. Overall, each product has its own characteristics and its packaging requirements may vary.

The choice of packaging materials may depend on the degree of protection required, compatibility with the formulation contents, the filling method, and its cost of production, presentation and the convenience of the packaging for the user such as size, weight, method of opening and reclosing and eligibility of printing. Many other factors that must be considered in packaging material selection include structural, economic/business, manufacturing, durability, environmental impact, and specialist properties for unique applications. Packaging containers may be primary or secondary and single-dose or multi-dose, depending on whether they are for immediate use after production of the finished product or otherwise for later use. Although synthetic materials are most commonly used as packaging materials recently use of biodegradable polymers in the manufacturing of packaging material is getting more attention because of their eco-friendly nature.

The selection of the proper packaging material depends on requirements such as protection against light, reactive gases, moisture, microbes, physical damage, pilferage and adulteration, presentation, identification, information, compatibility and convenience. There are a number of factors that influence selection of packaging material in respect of packaging features such as size, shape, design, surface graphics, colour schemes, labeling, materials, etc.

(1) **Physical Characteristics:** Packaging material selection decisions are influenced by certain physical characteristics of the product like the physical state, weight, stability, fragility, rigidity, surface finish etc. to be packaged.

(2) **Facilities available:** Selection of packaging material depends upon facilities required to convert these materials in to packaging components. For examples, pressurized dispenser requires special filling, sealing and labeling equipment.

(3) **Formulation components:** The product may react with the package such as the release of alkali from the glass or the corrosion of the metals and in turn the product is destabilized. Thus, stability and compatibility with the formulation contents are major concerns.

(4) **Stability:** Certain environmental factors like moisture, oxygen, light, flame, bacteria, fungi, chemical action, etc., affect stability of formulation. In addition, formulation

components may react with the package to release of constituents from the packaging material such as alkali from the glass or exhibit corrosion of the metals that in turn destabilizes the product. Therefore, stability of the formulation and compatibility with the formulation contents are major concerns in selecting packaging materials judiciously.

(4) **Economy:** In pharmaceutical packaging, quality of packaging is very important in view of product stability as well as marketing. Aesthetic value of product and cost are related parameters as good aesthetic (expensive) products usually use expensive packaging. Usually, packaging material selection is made without impairing the packaging requirements.

(4) **Convenience:** Packaging must necessarily possess the quality of convenience from the point of view of consumers, distributors and producers. Thus, apart from the functional requirement, a selection of packaging material is made based upon its certain features like suitability to produce packaging systems for ease to open and close, ease to dispense, ease to dispose of, ease to recycle, ease to identify, ease to handle, convenience to pack, convenience to stack, convenience to display, etc.

(5) **Miscellaneous criterion:** A packaging material selection may also be influenced by a number of other criterions, for example, if there is any statutory rule in respect of packaging, it will have to be abided by. The socio-cultural factors may also influence material selection. In addition, consumer attitudes also have to be given due consideration. The growth of consumerism in a number of countries suggests that selection should be made with meticulous care.

(6) **Regulations:** Packaging and labeling may be subject to government regulation in the countries. Some countries have specified packaging standards for certain products. If such regulations and standards are to be strictly followed, the products need to be packaged in containers made up of recommended materials.

(7) **Buyer Specifications:** In some cases, buyers like the exporters to give packaging specification. While incorporating such specifications it should also be ensured that packaging satisfies other requirements.

(8) **Socio-cultural criterion:** While designing the packaging for a product, socio-cultural factors relating to the important country like customs, traditions, beliefs etc, should also be considered.

(9) **Retailing characteristics:** The nature of retail outlets is a very important consideration packaging decision. For instance as pointed out earlier, in some of the foreign markets as a result of the spread of supermarkets and discount houses, a large number of products are sold on a self-service basis. The package has, therefore, to perform many of the sales tasks and hence it must attract attention, describe the product features, give the consumer confidence and make a favorable overall impression.

(9) **Environmental criteria:** Packaging material selection decisions are also influenced by certain environmental factors like weather and climate factors. The impact of such factors in the place where the product originates, while the product is in transit and while in the market etc., should be considered. The packaging material should be capable of withstanding the stresses and hazards of handling and transportation, stacking, storing etc., under diverse conditions globally.

(10) **Disposability:** Attention should also be paid to the aspects relating to the disposal of the containers. One of the qualities required for good package is that it could be easily disposed off or recycled. In some of the developing countries like India many packaging materials easily find some other use or are recycled. But the situation is different in other countries. Indeed, the disposal of packaging materials is causing environmental problems in a number of countries. Reusable packages have potential risk of misusing it for selling counterfeit products or any other irrational purpose.

Do you know?

- Materials such as paper, foil and fabric are used for labeling.
- It is possible to print directly on a bottle or other containers.

2.3 GLASS

Glass containers are commonly used for storing pharmaceutical products because glass possesses superior protective qualities. These containers are intended to come into direct contact with pharmaceutical products. The hydrolytic resistance, the resistance to release of soluble mineral substances into water, under the prescribed condition of contact between the interior surfaces of the container expresses the chemical stability of glass container for pharmaceutical use.

(a) Advantages of Glass:

1. Glass is impermeable to water vapors, air, etc.
2. It is available in various sizes and shapes.
3. It has efficient mechanical strength and rigidity.
4. It is transparent so the contents can be easily seen from outside.
5. It can be converted into light resistant form by mixing with metal oxides.
6. It has elegant appearance than plastic containers.
7. It withstands high temperature and pressure during sterilization.
8. It can be easily sealed to provide hermetic protection and is easily labeled.

(b) Disadvantages of Glass:

1. Glass is heavy thus increasing product transportation cost.
2. It is brittle and thus has high risk of cracking and breaking.
3. It easily leaches out alkali to aqueous product contents, if not chemically treated.

4. It is expensive to manufacture.
5. It has tendency of shedding some part of the silica into the formulation.

(c) Composition of Glass:

Glass is principally made up of silica (59-80%) with varying degree of calcium oxide (5-12%), sodium oxide (12-17%), aluminium oxide (0.5-3.0%), barium oxide, boric oxide, potassium oxide, and magnesium oxide and cullet. The high melting point of glass is due to the presence of silica. The melting point and melt viscosity of the glass is modified by the addition of oxides. The sand is almost pure silica; the soda-ash is sodium carbonate, and the limestone and calcium carbonate. Cullet is broken glass that is mixed with the batch and acts as a fusion agent for the entire mixture. The composition of glass varies and is usually adjusted for specific purposes. The most common cations found in glass are silicon, aluminium, boron, sodium, potassium, calcium, magnesium, zinc, and barium. The only anion of consequence is oxygen.

Many useful properties of glass are affected by the kind of elements it contains. Reduction in the proportion of sodium ions makes glass chemically resistant; however, without sodium or other alkalies, glass is difficult to melt and is expensive. Boron oxide is incorporated mainly to aid in the melting process through reduction of the temperature required. Lead in small traces gives clarity and brilliance, but produces a relatively soft grade of glass. Alumina (aluminium oxide), however, is often used to increase the hardness and durability and to increase resistance to chemical action.

(d) Process of Forming Glass Containers:

Glass containers are made using the following methods:

(1) Blowing: In this method compressed air is used to form the molten glass in the cavity of a mold.

(2) Drawing: This involves the pulling of molten glass through dies that shape the soft glass into ampoules, vials etc.

(3) Pressing: Glass container in this method is formed by the use of mechanical force which presses or forces the molten glass against the ride of a mold.

(4) Casting: In this method, the force of gravity or centrifugal force is used to initiate the formation of molten glass in the cavity.

Ampoules: Ampoules are thin-walled glass containers, which, upon filling are sealed by either tip or pull sealing method. The contents are withdrawn after rupture of the glass, or a single occasion only. These are great packaging for a variety of drugs. The filled in product is in contact with glass only and the packaging is 100% tamper proof. The break system, one point cut or the color break ring offer consistent breaking force. There are varieties of ampoule types available ranging from 0.5 to 50 mL. Up to three color rings can be placed on the stem of ampoule for identification. Printed ampoules with heavy metal free colors are also available. Vials are classified as Type B (straight stem), Type C (funnel tip) and Type D (closed).

Bottles, vials and syringes: These are more or less thick walled containers with closures of glass or of any other material such as plastic or elastomers. The contents may be removed in several parts at one or more times.

(d) Types of Glass:

According to their hydrolytic resistance glass can be classified in to the following types:

(1) Borosilicate glass (Type I): This is a type of glass container that contains 80% silica, 10% boric oxide, small amount of sodium oxide and aluminium oxide. It is a neutral glass and has a high hydrolytic resistance due to the presence of boric oxide. It has the lowest coefficient of expansion and so has high thermal shock properties and thus is a highly resistant glass. A substantial part of the alkali and earth cations are replaced by boron and/or aluminium and zinc. It is more chemically inert than the soda-lime glass. It is used to contain strong acids and alkalies as well as all types of solvents. The addition of approximately 6% boron forms type I glass that reduces the leaching action. Type I glass is suitable as packaging material for most preparations whether parenteral or non-parenteral. They can also be used to contain strong acids and alkalis.

(2) Treated soda-lime glass (Type II): The Type II glass which has high hydrolytic resistance is obtained from treatment of the inner surface of a type III glass with sulfur. When glass container is stored especially in a damp atmosphere or with extreme temperature variations for several months the wetting of the surface by condensed moisture results in salts being dissolved out of the glass. This process is called as blooming or weathering. Type II glass containers are made of commercial soda-lime glass which is de-alkalized or treated to remove surface alkali. The de-alkalizing process is known as sulfur treatment that prevents weathering of empty glass bottles. This glass may be exposed to an atmosphere containing water vapor and acidic gases which results in a reaction between gases and surface alkali, which makes it resistant to attack by water. The alkali leached from the glass appears on the inner surface as a sulfate bloom, which is removed when the containers are washed before filling. Thus, sulfur treatment neutralizes the alkaline oxides on the surface rendering it more chemically resistant. Type II glass has lower melting point when compared to Type I glass and so easier to mould. It is suitable for most acidic and neutral aqueous preparations whether parenteral or non-parenteral.

(3) Regular soda-lime glass (Type III): This is an untreated soda lime glass that contains silica 75%, sodium oxide 15%, calcium oxide 10%, small amounts of aluminium oxide, magnesium oxide, and potassium oxide. It has average or better than average chemical resistance. Aluminium oxide impacts chemical durability while magnesium oxide reduces the temperature required during moulding. This type of glass used for packaging of those parenteral products or powders that showed suitable stability in this glass. In addition, it can be used for packaging of non-aqueous parenterals and powders with the exception of freeze-dried preparations and for packaging of non-parenteral preparations.

(4) General purpose soda-lime glass (Type IV or NP): This glass is made up of soda-lime and is used for non-parenteral (NP) products such as those intended for oral or topical

use. This type of glass usually has low hydrolytic resistance and therefore it is not used for products that need to be autoclaved as its surface erosion increases with temperature. It is used to store topical products and oral dosage forms.

Coloured glass: Glass containers for drugs are generally available in clear flint or amber color. For decorative purposes, special colours such as blue, emerald green and opal may be used. Only amber glass and red glass are effective in protecting the contents of a bottle from the effects of harmful ultraviolet rays. The USP specifications for light-resistant containers require the glass to provide protection against 2900 to 4500 Angstroms of light. Amber glass meets these specifications, but the iron oxide added to produce this color could leach into the product. Therefore, if the product contains ingredients subject to iron-catalyzed chemical reactions, amber glass should not be used. Manganese oxide can also be used for amber glasses.

Glass containers are made by blowing, drawing, pressing and casting. The packaging components made up of glass include ampoules, bottles, vials and syringes.

Do you know?

- Holographic technology is the recent development in pharmaceutical packaging which provides a simplified means for consumers to infer authenticity of product.

2.4 PLASTIC

Plastic containers consist of one or more polymers together with certain additives, if necessary. These are long-chain polymers that can be melted, formed into a desired shape, and solidified during cooling. Features of plastic materials such as inexpensive, strong, durable, corrosion-resistance with high thermal and electrical insulation properties make them to be used widely in the pharmaceutical packaging industry. In addition, they can be easily molded into the desired shape and provide protection against contamination during storage and transportation.

For pharmaceutical purpose containers should be manufactured from the materials that do not include in their composition any substance that can be extracted by any contents in such quantities as to alter the efficacy or the stability of the product or to present a toxic hazard. The nature and amount of additives are determined by the nature of the polymer and the process used to convert the plastic into the package. It may contain certain additives such as antioxidants, stabilizers, plasticizers, lubricants, colouring matter and impact modifiers.

(a) Advantages of Plastics:

1. Easy to manufacture and are recyclable.
2. Available in various types of quality.
3. Freedom of design to which they lend themselves.
4. Extremely resistant to breakage and good puncture resistance.
5. It has wide consumer acceptance.

6. It is preferred over other packaging materials.
7. These are non-fragile and light in weight.
8. They have an excellent moisture and gas barrier properties.
9. They have low heat conductivity and good sealing properties.

(b) Disadvantages of Plastics:

1. Disposable plastics used in packaging for human consumption product contain harmful compounds with ecological risk.
2. Plastics are generally non-biodegradable.
3. Plastics generally have a low melting point and thus cannot provide desired level of protection against heat.
4. Plastics generally have a short useful life compared to metals.

(c) Types of Plastics:

(1) Polyethylene (PE): PE is available in three different grades namely low, medium and high density ranging from 0.91 to 0.96 g/mL. Physico-chemical properties such as clarity and translucency of this plastic varies with the density. High density polyethylene (HDPE) is the most crystalline material and is most widely used for the containers by the pharmaceutical industry for drug packaging because it offers good barrier against moisture but a relatively poor one against oxygen and other gases. The low, medium and high density PE has oxygen transmission of 500, 250-535 and 185, respectively. HDPE is most preferred in packaging of solid oral products. It is the material of choice with polypropylene (PP) as a polymeric material used in online blow fill seal technology.

(2) Polystyrene: The polystyrene (PS) is the clear rigid hard material with good tensile strength. The major limitation it has is its brittleness. Although it is resistant some of the mineral oils, water and alkali it solubilizes in the organic solvents. Since, it has fair permeation for moisture it is not commonly used for pharmaceutical packaging.

(3) Polycarbonate: The polycarbonate (PC) has good impact resistance and excellent dimensional stability. It has a low water absorption capacity and is heat resistant. Generally, it is used in making membrane filters, reusable bottles and sterilizable medical packaging.

(4) Polyvinyl chloride: Polyvinyl chloride (PVC) most widely used film forming plastic displaying ideal forming characteristics. PVC used in the film formation is called rigid PVC or RPVC as it is almost free of softening agents. It has very low water-vapor permeability. The advantages of using PVC are low cost and the ease of thermoforming. The poor barrier against moisture and oxygen ingress and negative environmental degradation due to its chlorine content are its major limitations. When it is used in blister packaging it does not contain any plasticizer and thus blisters offer structural rigidity and physical protection to the dosage form. The blister cavity soft to break or tear when pressed upon and for this reason the PVC sheet thickness is typically between 200 µm to 300 µm depending on the cavity size and shape. Most PVC sheets for pharmaceutical blisters are 250 µm in thickness. Typical values for the water vapor transmission rate (WVTR) of these PVC films are around

3.0 g/m^2/day measured at 38 °C/90 % RH and the oxygen transmission rate (OTR) is around 20 ml/m^2/day. In order to increase protective function of PVC film, it can be coated with PVDC or laminated with polychlorotrifluoroethylene. Multi-layer blister films based on PVC are often used for pharmaceutical blister packaging, whereby the PVC serves as the thermo formable backbone of the structure. PVC layer can be coloured with pigments and/or UV filters. The stabilizers, plasticizer, monomer, residue, modifiers, lubricants, catalytic residue are all that must be considered when PVC is used for pharmaceutical packaging.

(5) Polyvinylidene chloride: Polyvinylidene chloride (PVDC) is copolymer of vinyl chloride or vinyl acetate and vinylidene chloride. It is an excellent resistance to permeation by moisture and gas and mostly widely used as a coating. The coated PVC has characteristics similar to uncoated PVC except that the water vapor permeability of coated films is reduced by a factor of 5-10. The coating is applied on one side and usually faces the product and the lidding material.

(6) Polychlorotrifluoro ethylene: Polychlorotrifluoro ethylene (PCTFE) can be laminated to PVC to obtain very high moisture barrier. PVC-CTFE films have the lowest water-vapor permeability of all the films used for blister packaging. Because of some environmental concerns PVC is applied to PVC-CTFE film. Typical constructions used for pharmaceutical products are 250 µm PVC film laminated to 15 - 100 µm PCTFE film. Double layered structures are of PVC/PCTFE and triple layered laminates are of PVC/PE/PCTFE. Deeper cavities can be formed when used as triplex structures. Typical WVTR values are between 0.06 - 0.40 g/m^2/day.

(7) Cyclic olefin copolymers: Cyclic olefin copolymers (COC) or polymers (COP) in multilayered combinations with polypropylene (PP), PE, or glycol modified polyethylene terephthalate (PET) can provide moisture barrier to blister packs. Cyclic olefin resins are amorphous and have good thermoforming characteristics and thus are used in blister packaging as a thermoforming enhancer in combination with PP or PE. Films can be manufactured via co-extrusion or lamination. WVTR values of commercial cyclic olefin-based pharmaceutical blister films typically range from 0.20 to 0.35 g/m^2/day at 38 °C/90 % RH. These resins do not contain chlorine or other halogens in their molecular structure and is comprised solely of carbon and hydrogen.

(8) Polypropylene: PP is used as a support material for blister packages. The WVTR of uncoated PP is lower than PVC and is comparable to that of PVDC coated PVC. Problem with this polymer is its thermoforming processing. The temperature of thermoforming and subsequent cooling are critical parameters that need to be controlled. While warping of with PP packages need to be straightened before cartooning.

Do you know?

- Barcodes are used in the pharmaceutical industry to identify product throughout the supply chain.
- FDA stated that 'Track-and Trace' and 'Product Authentication' technologies should provide greater drug security.

2.5 METALS

Metal is the most versatile of all the materials used in the packaging. Metals are strong, relatively unbreakable, opaque, and impervious to vapors, gases, odour and microorganisms. It is used only in packaging of non-parental pharmaceutical products due to its particle shedding properties. They are usually resistant to temperature variation. As they react with some chemicals, metals require application of coating and lacquers to prevent chemical reaction and corrosion. The commonly used metals in pharmaceutical packaging include tin, aluminium and tinplate. Packs made from metal foil are strips and blisters and container packs are aerosol cans and gas cylinders. The collapsible metal tubes are attractive containers that permit specific amounts of formulation to be packed easily, with good reclosure and adequate environmental protection. The portion remaining in the tube upon dose removal is minimal and has low risk of contamination as metallic tubes do not suck back. Metallic tubes are light in weight, unbreakable, and are suitable for high-speed automatic filling operations.

(a) Advantages of Metals:

1. Some metals are light in weight.
2. Metals provide superior protection against contamination.
3. Form excellent tamper-evident containers.
4. Metals are strong and shatter proof.
5. Suitable for pressurized packaging.

(b) Disadvantages of Metals:

1. Metals are highly expensive.
2. Some metals are heavy in weight.
3. They show chances of toxicity.
4. They are reactive to certain chemicals and are susceptible to corrosion.

Table 2.2: Applications of Metal as Packaging Material

Package	Dosage form	Remarks
Strip, blister	Tablets, capsules	Polymer coated aluminium with various thickness are used to improve the sealability and stability.
Collapsible tubes	Ointments, creams, gels and other semisolids	The tubes with internal protective coating of polymers with and without spike are available.
Cans	Aerosols, inhalers, sprays, etc.	Pressure resistant and internal polymer coated aluminium containers are available.

(c) Types of metals:

(1) Aluminium: Aluminium has prominent protective characteristics against the effects of moisture, heat and light. It is used as laminate in strip and blister packaging and is costly component of laminate. In foils it is used at 99% purity and above with a gauge thickness of 0.6 to 0.40 μm. The foils made of this metal are annealed to give a soft foil with a dead fold property. Hard tempered (non-annealed) foils are used occasionally for push through lidding for blister packs. Lubricants are removed from hard foil by either solvent washing or controlled heating. Foils with nominal gauge variation of +8% are allowed to be used. This metal is used for packaging of tablets, capsules, and powders. Its light weight offers significant saving in the product shipping costs and when combined with tin it provides the attractiveness. The different types of aluminium packaging materials include lidding aluminium foil containers, lidding pharma foil, lidding packaging material, lidding blister foil, aluminium lidding foil poly, paper laminated foil, heat sealable lidding foil, triple laminate for ORS pouch and in strip packing, in collapsible tubes and Aluminium foil lidding. The excellent properties of aluminium foil provide a convenient, safe and versatile packaging system for variety of pharmaceutical products. Aluminium foil has superior barrier properties that totally excludes moisture, oxygen and other gases, microorganisms and light and thus maintains sensitive products during long term storage. In addition, it has dead fold and mechanical properties, a hygiene and safety, sustainability, and barrier property.

Various applications of aluminium as packaging material for pharmaceutical products includes blister packs, strip packs, sachets and pouches, heat-sealed membranes and closures and lidding materials. Alufoil is used as lidding material that provides the base upon which the final blister package is built. Its selection depends upon the size, shape, and weight of the product to be packaged. Types of lidding material used include hard aluminium, soft aluminium, paper aluminium and paper/PET/aluminium. Lidding material made of paper/PET/aluminium laminate is often called peel off–push through foil. The concept is to first peel off paper/PET/laminate from the aluminium and then to push the tablet through the aluminium. This kind of material is used predominately in the US. In addition, aluminium is used for making most of the metered dose aerosol suspension and emulsion containers. Aluminium may react with certain active ingredients and propellant in the formulation. This problem in many containers is solved by its internal surface coating with an epon- or -expoxy type resin.

(2) Tin: Tin is chemically inert of all collapsible tube metals. It is the more expensive than lead. Tin is the most ductile of these metals. Tin at 15% used in composition of metal used for collapsible tubes. Laminates of tin-coated lead provide better appearance and is resistant to oxidation. These laminates are cheaper compared to tin alone. The tin that is used for this purpose is alloyed with about 0.5% copper for stiffening.

(3) Lead: Lead has the lowest cost of all tube metals and is widely used for adhesives, inks, paints, and lubricants. When it is used as packaging material, about 3% antimony is added to increase hardness. Addition of aluminium hardens it when formed into a tube, and must be annealed to give it the necessary pliability.

Do you know?

- A tamper–resistant package is one having an indicator or barrier to entry which, if breached or trussing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred.

2.6 RUBBER

Rubber is used in the pharmaceutical industry to make closures, stoppers, cap liners and bulbs for dropper assemblies. Rubber components are made either from either natural or synthetic sources. Natural rubber has got good resealing, fragmentation and coring properties when compared to synthetic rubber. It is poor in respect to ageing and has chances of moisture and gas permeation. It is more susceptible to absorption of preservative systems and sterilization by multiple autoclaving is also not possible. Synthetic rubbers tend to reverse all of these properties.

The performance characteristics of rubber used in pharmaceutical applications are not intrinsic to the "pure" or "base" rubber but rather are imparted via its chemical modification. In order to produce the actual rubber materials used in pharmaceutical applications, the base elastomer is combined and/or reacted with a number of chemical agents or additives under harsh conditions of high temperature and pressure.

The main types of rubber used for pharmaceutical products include natural rubber, neoprene rubber, nitrile rubber, butyl rubber, chlorobutyl rubber, bromobutyl rubber, silicone rubber etc. Of these, silicone is the most expensive and inert, but is readily permeable to moisture, gases and absorbent to certain preservatives. Rubber components contain more additives and hence product-package interactions should be properly tested before they are used for parentral products. In the injectable drug products, rubber is used for many applications such closures for vials and bottles, seals and plungers for syringes and cartridges, gaskets in manufacturing equipment, and ports on plastic bags and intravenous administration sets. Rubbers are also used in aerosols and metered-dose pump systems.

Properties and Composition:

Physical and chemical properties of the rubber dictate the best choice of rubber for the product. The best choice of rubber also depends on how it will be used (e.g. as a closure, septum, plunger, rings) and on the properties of the drug product closed by the rubber. The physical properties considered in the selection of a particular rubber include elasticity, hardness (durometer), tendency to fragment, permeability to oxygen and/or water vapor transfer, pressure to puncture, coring, resealability, break force, vacuum retention, and specific leachables/extractables. Elasticity of the rubber is critical in establishing a seal with the lip and neck of a vial or other opening and in resealing after withdrawal of a hypodermic needle from a vial closure. The hardness provides firmness but not excessive resistance to the insertion of a needle through the closure, while minimal fragmentation of pieces of rubber should occur as the hollow shaft of the needle is pushed through the closure. While vapor transfer occurs to some degree with all rubbers, appropriate selection of ingredients makes it possible to control the degree of permeability.

Rubber closures are elastic and either translucent or opaque. They are homogeneous and practically free from flash and adventitious materials. The rubber closure is used primarily for multiple dose vials and disposable syringes. Rubber closure may be classified into two types:

1. Type I closures: Meets the strictest requirements and thus are most preferred.
2. Type II closures: These have mechanical properties suitable for special use.

When the closure chosen for use is in contact with preparation it must not be adsorbed onto the surface of the closure and do not migrate into or through the closure to an extent sufficient to affect the preparation adversely. For example, when the rubber stopper comes in contact with parenteral solution, it may absorb active ingredient, antibacterial preservative or other materials and one or more ingredients of the rubber may be extracted into the liquid. These extractives could interface with chemical analysis of the active ingredient; affect the toxicity or pyrogenicity of the injectable product, interact with the drug preservative to cause inactivation and may affect the chemical and physical sterility of the preparation.

Elastomers:

Rubber formulations contain a variety of components. The base material for the rubber is the elastomer that is composed of either natural or synthetic rubber. The elastomer determines most of the physical and chemical characteristics of the rubbers. The source of the elastomer material is natural latex rubber liquid obtained from the Hevea brasiliensis tree, but today, an increase in demand for rubber led to developments in the production of synthetic rubbers. Butyl rubber is the most commonly used elastomer for pharmaceutical applications today because of its superior oxygen/moisture barrier. Neoprene is a halogenated synthetic rubber, which is available for more oil based products.

The elastomers are produced from natural or synthetic substances by cross-linking of elastomers, with appropriate additives through polymerization, polyaddition or polycondensation. The nature of the additives depends on the properties required for the finished package component. The additives include curing agent, an activator, filler, as well as additional compounds to control cure rate, colour, and resistance properties. The curing agent, or vulcanizing agent, forms the cross-links in the rubber that provide the shape, the elasticity, and the resiliency. Sulfur is the most common curing agent for elastomers with chemically unsaturated backbones. An activator, typically a metal oxide with a fatty acid, is used to accelerate the rate at which the sulfur reacts with the unsaturated polymer. The most common activator is zinc oxide combined with stearic acid. An accelerator (sulfenimide) and a retarder (benzoic acid, salicylic acid and phthalic anhydride), can be added to control the rate of vulcanization. Fillers are added to reduce tack, adjust color, and often to increase hardness and durability. Common fillers include carbon black, clay, calcium carbonate, and precipitated silica. Additional additives can include antioxidants and antiozonates as well as colorants. The color depends on the additives used.

(a) Advantages of Rubber:

1. Rubber is easy to use.
2. Rubber is inexpensive.
3. It exhibits good abrasion resistance and is elastic.
4. It has ability to be removed easily from an article.
5. They are very soft and stretchable.
6. Softer rubbers experience less coring and reseal better.
7. Harder rubbers are easier to process on high speed packaging lines.

(b) Disadvantages of Rubber:

1. Low-cost rubbers generally shrink.
2. Rubber has offensive odour.
3. Some rubbers are sensitive to chemicals, and do not have a long shelf life.
4. They are brittle upon long exposure to heat.

Do you know?

- Pre-filled syringes (PFS) constitute one of the fastest growing markets in the drug delivery and packaging sectors.

Manufacturing:

The basic steps in the manufacture of rubber closures involve:

1. Raw materials are tested for identity and purity.
2. Formulation ingredients are weighed within ± 1% tolerances.
3. Batch ingredients are mixed and tested to insure cure characteristics.
4. The mixture is placed in an extruder to create pellets, strips, or sheets and molded by injection, compression, or transfer.
5. The molded sheets (stoppers) are trimmed and washed to remove trim and mold lubricants.
6. The stoppers are baked and autoclaved, if applicable.
7. The stoppers are tested for conformance by chemical and physical testing and are packed.

The two major steps in the production of rubber products are the compounding of the components followed by curing. In the compounding process, the rubber is masticated, or broken down by heat and shearing with a mixer. Mastication breaks down the polymer, increasing its viscoelasticity, and enables the incorporation of additives such as fillers. Following mastication, the remaining additives, with the exception of the curing agents are added and mixed. Remilling may follow if required to improve dispersion of additives or to modify viscosity. The curing system is added during the finish mixing step and the hot

mixture is then extruded through a die to form pellets or through a pair of rollers to form a sheet. The rubber is further formed by injection molding or more commonly for stoppers, compression molding, and is then cured or vulcanized. Vulcanization consists of three stages; induction, curing and reversion.

(a) Cleaning: Rubber closures are cleaned and depyrogenated by rinsing with numerous amounts of Water for Injection and, if necessary, a cleaning agent like sodium hydroxide, Liquid Safe-Kleen, or tri-sodium phosphate. Many rubber formulations contain polymer surfaces that do not require siliconization and process without difficulty. However, if siliconization is required, it is done prior to sterilization, but after the depyrogenation procedure, and usually in the stopper washer. A pre-determined amount of silicone is added to the stopper washer during a specified period of the washing cycle.

(b) Sterilization: Sterilization of rubber closures is done by steam sterilization in an autoclave using a validated cycle. Rubber plungers used in pre-sterilized, ready-to-fill syringes are sterilized by gamma radiation.

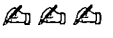
(c) Qualification: Physico-chemical and toxicological tests for evaluating rubber closures are described in USP. *In-vitro* biological reactivity tests for rubber include the agar diffusion test, the direct contact test, and the elution test. *In-vivo* biological reactivity tests include the systemic injection test, the intracutaneous test, and the implantation test.

(d) Siliconization: Rubber closures must be 'slippery' in order to move easily through a rubber closure hopper and other stainless steel passages until they are fitted onto the filled vials. Traditionally, rubber materials are 'siliconized' (silicone oil or emulsion applied onto the rubber) in order to provide lubrication.

REVIEW QUESTIONS

1. Define package, packaging and pharmaceutical packaging.
2. What are reasons for pharmaceutical product packaging?
3. Classify packaging materials with suitable example from each class.
4. What is primary, secondary and tertiary package? Give examples of each.
5. List and describe components of pharmaceutical packaging.
6. What are criterions for selection of pharmaceutical packaging material?
7. What are advantages of pharmaceutical packaging?
8. What is composition of glass? How is it produced?
9. What are its ideal requirements as a packaging material?
10. What are advantages and disadvantages of glass as a packaging material?
11. Discuss various types of glass used as a packaging material in pharmaceuticals.

12. What is general purpose glass? What are its uses?
13. Which type of glass is used for parenteral products? Why?
14. What is coloured glass? How is it manufactured?
15. What is plastic? What are its ideal properties for packaging of pharmaceuticals?
16. What are advantages and disadvantages of plastic?
17. Enlist types of plastic materials used as packaging materials.
18. Discuss most widely used plastic in pharmaceutical packaging.
19. What is metal type of packaging? Give its ideal characteristics.
20. What are advantages and disadvantages of metals?
21. Discuss various metals used in pharmaceutical packaging.
22. Describe aluminium as metal of choice in pharmaceutical packaging.
23. What is rubber? What are its ideal properties?
24. Discuss types of rubber used in pharmaceutical packaging.
25. What are advantages and disadvantages of rubber?
26. Discuss manufacturing of rubber closure.
27. What type of packaging components are made up of glass, metals and rubber?



Chapter ...3

PHARMACEUTICAL AIDS

♦ **LEARNING OBJECTIVES** ♦

After completing the chapter, students will be able to:

- Define pharmaceutical aid and classify them.
- Know examples of pharmaceutical aids and understand their functions.
- Know applications of organoleptic pharmaceutical aids in various preparations.
- Define preservatives; know its examples, functions and uses.

3.1 INTRODUCTION

A vast number of chemical substances are extensively used in the manufacturing and processing of pharmaceutical products and devices. Majority of these substances have little or no therapeutic value and are necessary in the manufacture of various dosage forms to perform various functions. Such substances are known as "pharmaceutical aids" or "pharmaceutical necessities". Pharmaceutical aids can be defined as the inert substances which have no or little pharmacological effect but are essential to be used in the preparation of pharmaceutical dosage forms. These substances may be required to perform certain functions during successful manufacturing, storage and transportation, and use of pharmaceutical products. These aids may remain in the final product, do not exert any specific action on the body upon administration of the product or are removed during processing. They are in direct contact with the drug at some stage within the formulation. When used in formulations they should be of high quality similar to drugs and are subjected to similar quality control testing. Pharmaceutical aids can be classified into various categories as absorbents, adsorbents, acidifiers and alkalisers, antioxidants, binders, buffers, buffering agent, colouring agents, disintegrating agents, diluents, desiccants, emulsifying agents, filter aids, flavouring agents:, humectants, lubricants, ointment bases, preservatives, sweetening agents, texturing agents, thickening agents, solvents, suspending agents, tonicity modifiers, vehicles, etc.

3.2 ORGANOLEPTIC PHARMACEUTICAL AIDS

Organoleptic substances promote appearance and palatability of pharmaceutical dosage form and contribute to the acceptance of the pharmaceutical products. The flavouring, sweetening and colouring agents are grouped together as organoleptic aids. Bitter and arid taste drugs are avoided by patients through oral route because of unpleasant taste and

odour as well as colour. Thus, organoleptic aids are incorporated to improve their colour, flavour and taste, especially for products prescribed for pediatric and geriatric patients.

Organoleptic pharmaceutical aids are the components which have no therapeutic value but these are essential to formulate any drug into its products with attractive look for easy acceptability by the patients.

Do you know?

- ❖ Many times pharmaceutical aids can also be known as additives, excipient or inactive ingredients.
- ❖ Pharmaceutical aids are subjected to similar quality control standards as drug.

3.2.1 Colouring Agents

Colouring agents are added to provide distinctive colour with pleasing appearance or elegance to the dosage form. Colour helps the manufacturer to control the product during its preparation as well as serving as a means of identification to the user. Colouring agents may be soluble in the solvent system or suspended as insoluble powders. All colouring agents used in pharmaceutical formulations must be approved and certified by FDA as per D&C Act 1940.

Various types of colouring agents are:

(1) Natural colours: Natural colours are obtained from minerals, plants and animals.

(i) Mineral: Minerals are frequently termed as pigments and are used to colour lotions, cosmetics and other preparation for internal and external use.

Titanium dioxide (TiO_2): Naturally occurring oxide of titanium is used in cosmetics and skin care products as a pigment and a thickener. It is mostly commonly used in sunscreen products because of its strong UV light absorbing capabilities and its resistance to discolouration in UV light.

Ferric oxide: Iron oxide is a mineral produced by fine grinding of ores. Iron oxide is light fast, chemically stable and colour controlled within narrowly defined parameters. Red and yellow iron oxide is used in manufacturing of coloured cosmetics.

(ii) Plant: The colour constituents from plants are obtained through extraction.

Indigo: It is obtained from plant *Indigofera tinctoria*. The colour spectrum is 420-450 nm. The colour wavelength is in between blue and violet.

β-Carotene: It is a carotenoid comes under natural pigments found in carrots, spinach and broccoli. The orange colour is masked by green colour of chlorophyll. Carotenoid, a source of vitamin A, can protect body against oxidative damage and can protect the product from UV light.

(iii) Animal colours: These are obtained from animal source.

Tyrian Blue: This is obtained from oxidizing of a colourless secretion from the gland of snails.

Cochineal: This is obtained from an insect Coccus cactus and has a brilliant red colour (carminic acid).

(2) Synthetic Colours: Synthetic colouring agents are used in pharmaceutical and cosmetic products to enhance their appearance without any toxicity. It is mainly used today under D&C Act 1940.

(i) Caramel: It is a dark brown material obtained by controlled thermal application on carbohydrates. It is commonly known as burnt sugar. The process of caramelization consists of heating sugar slowly to around 170 °C (340 °F). As the sugar heats, the molecules break down and re-form into compounds with a characteristic colour and flavour.

(ii) Coal tar dyes: These are obtained from petrochemicals and coal. These are mostly aromatic azo dyes. Coal tar dyes are used in medicated shampoo, soap and ointment, etc.

(iii) Lake dyes: These are aluminium or calcium salts of any water soluble colour. A lake pigment is manufactured by precipitating a dye with metallic salt. Lake pigments are organic and are fugitive because the dyes involved are unstable when exposed to light. Many lake pigments are azo dyes which have sulfonate and carboxylate substituent, which confer negative charge to the chromospheres.

Do you know?

- Pharmaceutical aids have no therapeutic value and are used in formulation for various functionalities.
- Pharmaceutical aids can not only provide some dosage forms of drug but also increase therapeutic effects and reduce side effects.

3.2.2 Flavouring agents

Flavouring agents are usually used to mask the saline, bitter, sour, sweet taste sensations. Flavouring agent is required in order to increase the patient acceptance and are significant particularly in orally administered liquid dosage forms, chewable tablets of antacids, vitamins and antibiotics. Usual strength at which these agents used is 0.5 to 0.75%. They are usually stored at 15-30 °C with relative humidity of 45%. The selection of the flavouring agents depends on taste of drugs and the age of the patient, for examples, children like sweet candy like preparations with fruit flavour but adults may prefer less sweet preparation with a tart. The elderly persons may have liking for wine flavour. Some flavouring agents are more effective over others in masking the particular taste. As an example, cocoa flavours are preferred for masking taste of bitter drugs; citrus flavour is used to combat sour or acid taste of drugs; and cinnamon, orange and raspberry flavour for saline taste drugs. The chewable or effervescent tablets need flavours as well as sweetening agents to improve patient acceptance.

As the flavouring agents are often thermolabile and volatile, the time of incorporating them in formulations is critical. They cannot be added to formulation when hot. In case of liquid dosage forms these agents are added to the solvent or vehicle of the formulation in which it is most soluble or miscible. The water soluble flavouring agents are added to the aqueous component of the formulation and poorly soluble flavouring agents are added to

the alcoholic or other non-aqueous solvent of the formulation. In multi-component systems, the appropriate solvent level of the flavouring agent is essential to keep them in solution.

Examples: Volatile oils such as cocoa, citrus, cinnamon, orange and raspberry, clove, fennel, orange, wintergreen oil, and rose, jasmine, and lavender are used as flavours.

3.2.3 Sweetening agents

Sweetening agents are used to impart sweet taste to the bitter pharmaceutical formulation. These agents need to be dissolved either when taken as solution or dissolved in saliva. It is used to impart acceptable taste to the oral formulation because all drugs for oral use may not have pleasant taste and often unpleasant taste is to be masked.

Sucrose: Sucrose is soluble in water and is easily available in highly purified form. It is physico-chemically stable at pH 4-8. It is frequently used in conjugation with sorbitol, glycerin and other polyols which reduce the tendency of sucrose to crystalline.

Liquid glucose: Liquid glucose, also known as glucose syrup or confectioner's glucose, is syrup made from the hydrolysis of starch. It can also be made from potatoes and wheat, and less often from barley, rice and cassava. Glucose syrup contains varying amounts of glucose, maltose and higher oligosaccharides, depending on the grade, and can typically contain 10% to 43% glucose. Glucose syrup is used to sweeten, soften texture and add volume.

Saccharin: It is an artificial (synthetic) sweetening agent which is almost 500 times sweet as sugar but gives a bitter taste aftertaste. It is available as saccharin sodium and saccharin calcium. Its main limitation is its carcinogenic property which makes it a secondary choice.

Cyclamates: Sodium cyclamate is an artificial sweetener, 30–50 times sweeter than sucrose. It is often used with saccharin in a ratio of 10:1 to mask the off-tastes of both sweeteners. It is cheaper than most sweeteners, including sucralose, and is stable under heating. Now, being a carcinogenic, it has been banned.

Aspartame: It is the methyl ester of aspartic acid and phenyl alanine. It is hygroscopic in nature and thus has less stability in presence of moisture.

Sucralose: It is a non-nutritive non-caloric sweetener. It is about 320 - 1,000 times sweeter than sucrose, twice sweeter than saccharin, and three times sweeter than aspartame. It is stable under heat and over a broad range of pH conditions and thus it is used for products that require a longer shelf life. It is a sweetener of choice due to its favorable low-calorie, higher degree of sweetness, stability and safety properties.

3.3 PRESERVATIVES

Preservative is a substance commonly added to pharmaceutical product in order to prolong its shelf life. The addition of preservative to products that have higher water content is essential for avoiding alteration and degradation by microorganisms during storage. Preservatives are added in pharmaceutical preparation to inhibit growth of bacteria, yeasts,

or molds that can cause disease. Chemical preservation cannot totally keep products away from spoiling, but they slow down the spoiling process caused by microorganisms. Frozen and canned products often do not contain any preservatives.

Ideal Properties of Preservatives:

1. It should be non-irritant, non-toxic and physico-chemically stable.
2. It should be compatible with other ingredients used in formulation.
3. It should act as antimicrobial agent and exert wide spectrum of activity.
4. It should be potent and act effectively in small concentrations.
5. It should maintain activity throughout product manufacturing, shelf life and usage.

3.3.1 Definition

A preservative is a natural or synthetic chemical that is added to pharmaceutical products to prevent decomposition by microbial growth or by undesirable chemical changes.

3.3.2 Types with Examples and Uses

(1) Based on mechanism of action:

(i) Antioxidants: The agents that prevent oxidation of drugs which otherwise undergo degradation due to oxidation as they are sensitive to oxygen.

Examples: Vitamin E, vitamin C, butylated hydroxyanisole, butylated hydroxytoluene, etc.

(ii) Antimicrobial agents: These are agent that acts against gram positive and gram negative microorganism responsible for causing degradation of pharmaceutical preparation.

Examples: Sodium benzoate, sorbates, methyl paraben, propyl paraben, etc.

(iii) Chelating agents: These are agents which form the complex with the pharmaceutical ingredient and prevent degradation of pharmaceutical formulation.

Examples: Disodium ethylenediamine tetraacetic acid (EDTA), polyphosphates, citric acid, etc.

(2) Based on source:

(i) Natural preservatives: These are substances obtained from natural sources such as plant, mineral sources and animals which act as antimicrobial agents.
Examples: Neem oil, sodium chloride, lemon, honey, etc.

(ii) Artificial preservatives: These are agents prepared by chemical synthesis which acts against various micro-organisms in small concentrations.

Examples: Benzoates, sodium benzoate, sorbates, propionates, nitrites, etc.

Ethyl alcohol: Ethanol is bactericidal in aqueous mixtures at concentrations between 60% and 95% v/v; the optimum concentration is generally considered to be 70% v/v. Antimicrobial activity is enhanced in the presence of eidetic acid or edentate salts. Ethanol is inactivated in the presence of nonionic surfactants and is ineffective against bacterial spores.

Tocopherols: Alpha tocopherol is a source of vitamin E, and is a commercially available preservative. Amongst tocopherols the beta, delta, and gamma tocopherols are considered to be more effective as antioxidants. Alpha-tocopherol is a highly lipophilic compound, and is an excellent solvent for many poorly soluble drugs of wide spread regulatory acceptability. Tocopherols are of value in oil- or fat-based pharmaceutical products and are normally used in the concentration range 0.001-0.05% v/v. Its antioxidant effectiveness can be increased by the addition of oil-soluble synergists such as lecithin and ascorbyl palmitate.

Sodium benzoate: Sodium benzoate is used as preservative that becomes effective at concentrations of 0.02- 0.5% in oral medicines, 0.5% in parenteral products, and 0.1-0.5% in cosmetics. It is effective over a narrow pH range and is used in preference to benzoic acid due to its greater solubility. It may impart an unpleasant flavour to a product.

Potassium benzoate: Potassium benzoate's preservative efficacy increases with decreasing pH and is most effective below pH 4.5. However, at very low pH undissociated benzoic acid may produce a perceptible taste in products. It is used as an alternative to sodium benzoate in applications where low sodium content is desirable.

Methyl paraben: Methyl paraben is used in almost all types of pharmaceutical formulations. It may be used either alone or in combination with other parabens or with other antimicrobial agents. Methyl paraben is most effective against yeasts and molds over a wide range of pH and have a broad spectrum of antimicrobial activity. Antimicrobial activity increases as the chain length of the alkyl moiety is increased, but aqueous solubility decreases; therefore a mixture of parabens is frequently used to provide effective preservation. Its preservative efficacy can also be improved by the addition of propylene glycol (2-5%), or by using parabens in combination. Sodium salt of paraben is more frequently used in formulations.

Propyl paraben: Propyl paraben is a benzoate ester (propyl ester) of 4-hydroxybenzoic acid. It is typically used in many water-based cosmetics, such as creams, lotions, shampoos and bath products. It can also be used as a food additive. It acts as an antifungal agent and an antimicrobial agent.

Do you know!

Pharmaceutical aids also includes....

Thickening agents	Lubricants	Disintegrating agents
Filter aids	Suspending agents	Acidulants
Emulsifying agents	Diluents	Lubricants
Binders	Antioxidants	Wetting agents

REVIEW QUESTIONS

1. What are pharmaceutical aids? What is its significance in pharmaceuticals?
2. Classify and describe pharmaceutical aids with examples.
3 What are ideal properties of pharmaceutical aids?
4. What are organoleptic pharmaceutical aids? Classify them with examples.
5. What are colouring agents? What are its uses in pharmaceutical formulations?
6. Classify colouring agents with examples.
7. Describe various colouring agents used in pharmaceutical formulations.
8. What are flavouring agents? What are its uses in pharmaceutical formulations?
9. Classify flavouring agents with examples.
10. Describe various flavouring agents used in pharmaceutical formulations.
11. What are sweetening agents? What are its uses in pharmaceutical formulations?
12. Classify sweetening agents with examples.
13. Describe various sweetening agents used in pharmaceutical formulations.
14. What are preservatives? What are its uses in pharmaceutical formulations?
15. Classify preservatives based on mechanism of action giving suitable examples.
16. What are ideal properties of preservatives?
17. Describe various preservatives used in pharmaceutical formulations.

Chapter ...4

UNIT OPERATIONS

♦ **LEARNING OBJECTIVES** ♦

After completing the chapter, students will be able to:

- Gain basic knowledge of unit operations and processes employed in functioning of pharmaceutical industries.
- Define, differentiate and understand concepts between important pharmaceutical unit operations.
- Understand the working principles, design and working of industrial equipment to develop operational skills.
- Identify suitability of equipment to employ them for appropriate processing to conserve energy.

4.1 INTRODUCTION

Pharmaceutical industry uses various unit operations such as size reduction, size separation, drying, filtration, extraction, etc., to process materials to convert them into products. These unit operations are based upon certain physical, chemical and engineering principles. An understanding of these operating principles is a key to designing a robust drug product manufacturing process. A thorough knowledge of these principles can become useful in the design, development and scale-up of pharmaceutical unit operations to monitor, control, and evaluate these individual unit operations and the quality of the material produced from them. Unit operations gives an idea about science related to specific physical operation; different equipment and its design, material of construction and working; and calculation of various physical parameters.

4.2 SIZE REDUCTION

Pharmaceutical powders are classified as monodispersed (particles of same size) as well as polydispersed (particles of different sizes). Particles of monodispersed type are ideal for pharmaceutical applications whereas polydispersed powders create considerable difficulties in their processing for production of dosage forms. In order to obtain uniform size particles, powders are to be reduced in their size by size reduction. Size reduction involves techniques to create new surfaces and increase surface area by adding energy proportional to the bonds holding the feed particles together.

(a) Definition:

Size reduction is defined as a process of reducing large solid unit masses (vegetable or chemical substances) into small unit masses, coarse particles or fine particles. Comminution is the generic term used for size reduction and includes different operations such as crushing, grinding, milling, mincing, and dicing.

(b) Objectives:

The main objective of size reduction is to produce smaller particles from larger ones. Smaller particles are the desired product either because of their large surface area or because of their shape, size, and number. Other objectives of size reduction include:

(a) To increase surface area of solids to enhance the rate of dissolution, solubility, binding strength and dispersion properties.

(b) To perform separation of two constituents in cases where one is dispersed in small isolated pockets.

(c) To meet stringent specifications of the sizes of commercial products.

(d) To accomplish and improve intimate mixing of solids in a solid-solid operation.

(e) To increase the therapeutic effectiveness of certain drugs.

(f) To improve physical appearance, flowability, and compression and dose uniformity of products.

(g) To enhance stability of dispersed system such as emulsions and suspensions.

Do you know!

- Mechanisms involved in size reduction are compression, impact, attrition and cutting,

4.2.1 Hammer Mill

A hammer mill is an essential machine in the pharmaceutical industries. It is used to crush, pulverize, shred, grind and reduce material to suitable sizes.

(a) Principle:

The working principle of hammer mill is simple to understand. The principle is illustrated in Fig. 4.1 (a). It only requires choosing an appropriate motor, crushing hammers/knives and material you intend to crush. It operates on the principle of impact between rapidly moving hammers mounted on rotor and the stationary powder bed. The material is crushed and pulverized between the hammers and the casing and remains in the mill until it is fine enough to pass through a sieve which forms the bottom of the casing. Both brittle and fibrous materials can be handled in hammer mills, though with fibrous material, projecting sections on the casing may be used to give a cutting action.

(b) Construction:

Hammer mill has five main parts. Fully assembled pharmaceutical hammer mill is showed in Fig. 4.1 (b). Normally, the number of parts may vary depending on the complexity of the

machine design. Every part in the hammer mill plays an integral role in the overall working of hammer mills. However, the milling process mainly takes place in the crushing chamber. It consists of a stout steel casing in which a central shaft is enclosed to which four or more swinging hammers are attached. When the shaft is rotated by motor the hammers swing out to a radial position. On the lower part of the casing a sieve of desired size is fitted which can be easily replaced according to the particle size required. The material is crushed and pulverized between the hammers and the casing and remains in the mill until it is fine enough to pass through a sieve. Some mills consist of projecting sections on the casing used to give a cutting action if fibrous materials are to be processed. The hammer mills are available in various size, designs and shapes. In pharmaceutical industry, they are used for grinding dry materials, wet filter cakes, ointments and slurries.

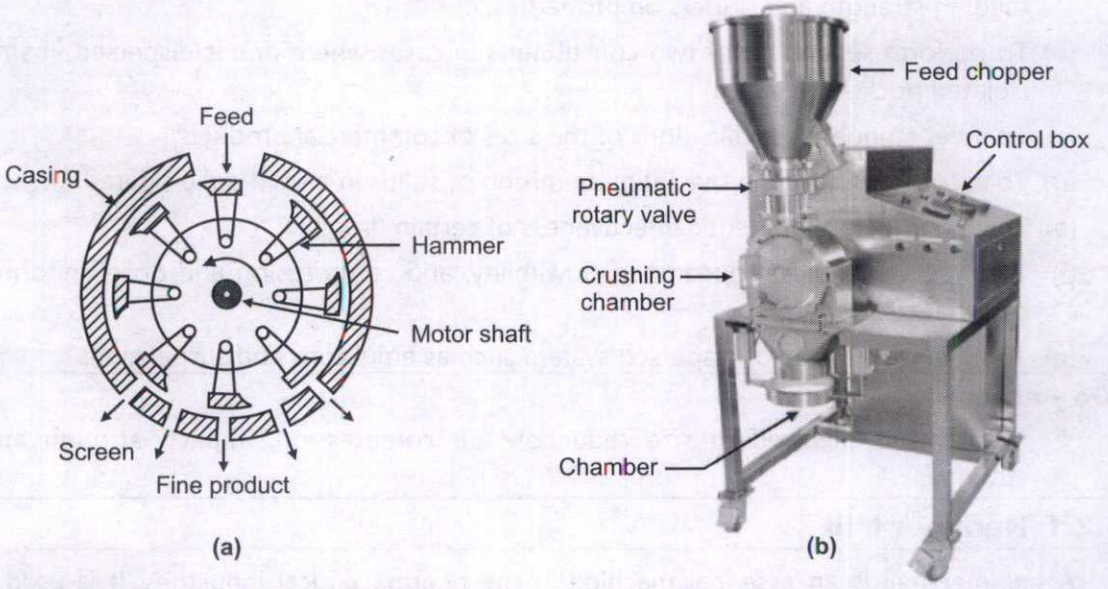


Fig. 4.1: Hammer Mill (a) Schematic and (b) Industrial Equipment

(c) Working:

Feeding mechanism refers to the process by which particles enter the crushing chamber. Depending on the design of the hammer in mill, it may use either gravity or a metered feeding system. Metered feeding systems are used when product uniformity is a major concern as they eliminate all possible variables that may cause output product inconsistencies. In the gravity feeding system, the milling machines solely depend on the gravitational force that helps to feed particles into the crushing chamber. Users can switch ON/OFF the machine and may control the feeding system or motor speed from the control box. Some pharmaceutical milling machines has display panel to monitor all parameters. This mill operates at a high speed from 2,500 to 60,000 r.p.m. The swinging hammerheads are attached to a rotor that rotates inside a hard casing. In most cases, hammers are mounted on horizontal shafts where they may rotate either clockwise or anti-clockwise. A rotor is the rotating shaft coupled to an electric motor. The hammers come in different

styles and shapes. The motor belt can cushion it from shock and allows for accurate speed adjustment. The output size of the particles depends on the sieve variation. Hammer mills may have over 12 different types of sieve meshes.

(d) Applications:

(1) Hammer mills can be used to crush fibrous materials using its cutting edges.

(2) It can be used to fracture brittle material by impact of blunt hammers.

(3) It can be used to produce intermediate grades of powders of almost all substances.

(4) It is suitable for powdering of barks, leaves, roots, crystals and filter cakes.

(5) Used in granulation where to cut damp mass into granules.

4.2.2 Ball Mill

A pharmaceutical ball mill is a type of grinder used to grind and blend materials while manufacturing various dosage forms. The size reduction in ball mill is done by impact as the balls drop from near the top of the shell. Ball mills are used primary for single stage fine grinding, regrinding, and as the second stage in two stage grinding circuits. According to the need ball mill can be either for wet or dry designs. Ball mills have been designed in standard sizes of the final products between 0.074 mm and 0.4 mm in diameter.

(a) Principle:

The size reduction in ball mill is a result of fragmentation mechanisms (impact and attrition) as the balls drop from near the top of the shell. Mixing of feed is achieved by the high energy impact of balls. The energy levels of balls are as high as 12 times the gravitational acceleration. Rotation of base plate provides the centrifugal force to the grinding balls and independent rotation of shell to make the balls hit the inner wall of the shell. The operating principle of the ball mill involves feeding of material through the central hole into the drum (shell) that moves along with grinding media (balls). As the shell rotates the balls are lifted up on the rising side of the shell and cascade down (or drop down on to the feed) from near the top of the shell. The material grinding occurs during impact of falling grinding balls and abrasion of the particles between the balls. In ball mill depending on the rotational speed following possible modes of the grinding media motion could be achieved.

(a) Low speed: Speed mode with a rolling of grinding balls without flight.

(b) Mixed mode (Cascade mode motion): Speed mode with a partial rolling and a partial flight of grinding balls.

(c) High speed: Speed mode with circular motion of balls with no fall.

The speed of the rotation is more important. At a low speed, Fig. 4.2 (a), the mass of the ball slides or rolls over each other with inefficient output. At a high speed, Fig. 4.2 (b), the balls are thrown out to the walls by centrifugal force. Since at this speed there is absence of

any impact or attrition no grinding occurs. Compression by the ball against the shell wall is not enough for comminution. But at 2/3rd of the speed (50 to 80% of the critical speed), Fig. 4.2 (c), the centrifugal speed force just occurs with the result that the balls are carried almost to the top of the mill and then fall to the bottom. This way, the maximum size reduction is affected by the impact of particles between the balls and by attrition between the balls.

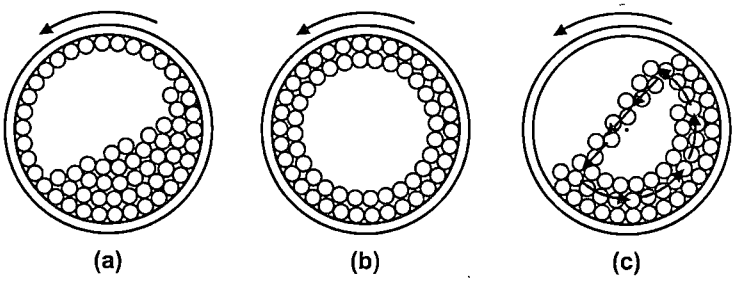
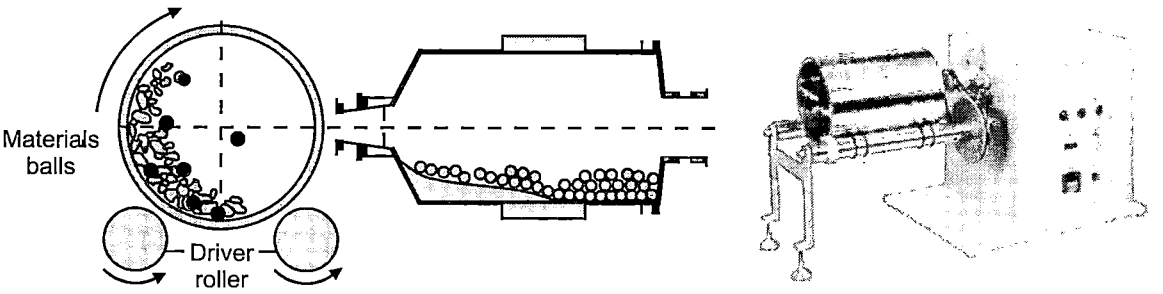


Fig. 4.2: Cascade Operation in Ball Mill (a) Low Speed (b) High Speed (c) Correct Speed

(b) Construction:

Ball mills are designed in standard sizes of the final products between 0.074 mm and 0.4 mm in diameter. The most commonly used ball mills used for different pharmaceutical applications are pebble ball mill and vibrating ball mill. A typical ball mill consists of a hollow cylindrical shell (drum) containing balls mounted on a metallic frame such that it can be rotated along its longitudinal axis, Fig. 4.3. The axis of the shell may be either horizontal or at a small angle to the horizontal. It is partially filled with balls, which may be made of chrome steel, stainless steel or ceramic. The balls which could be of different diameter occupy 30 - 50% of the mill volume and its size depends on the feed and mill size. The ball size depends on the feed and the diameter of the mill. The inner surface of the cylindrical shell is usually lined with an abrasion-resistant material such as manganese steel or rubber. The coated metallic drum provides attrition force. The length of the mill is approximately equal to or slightly greater than its diameter.



(a) Principle operation **(b) Industrial mill**

Fig. 4.3: Pharmaceutical Ball Mill

(c) Working:

Ball mills differ to an extent in their operating principle. They also differ in their maximum capacity of the milling vessel, ranging from 0.010 liters for planetary ball mill, mixer mill or vibration ball mill to several 100 liters for horizontal rolling ball mills. Large to medium ball mills are mechanically rotated on their axis, but small ones normally consist of a cylindrical capped container that sits on two drive shafts. The steps involved in the working process of ball mill are as follows:

(1) Initial stage: Powder particles get flattened by the collision of the balls. It leads to changes in the shapes of individual particles or cluster of particles being impacted repeatedly by the milling balls with high kinetic energy.

(2) Intermediate stage: A significant change in size of material occurs in comparison with those in the initial stage.

(3) Final stage: Reduction in particle size takes place to fine size. The microstructure of the particle also appears to be more homogenous at microscopic scale than those at earlier two stages.

(4) Completion stage: The powder particles possess an extremely deformed metastable structure.

(d) Applications:

(1) Small capacity ball mills are used for wet grinding, for example, suspensions.

(2) The high capacity ball mills are used for milling ores.

(3) Ball mills are an efficiently used in grinding many brittle, sticky and amorphous materials into fine powders.

(4) Ball mills are used for grinding of hard and abrasive as well as wet and dry materials for pharmaceutical purpose.

(5) These mills are used to grind powders for ophthalmic and parenteral products, milling of pigments and insecticides for industrial purpose.

(8) Rubber ball mills are used for blending of explosive materials.

(9) Ball mills are used to effectively increase solid-state chemical reactivity.

Advantages of ball mill includes simple design, ease of examination, change of abraded spare parts, reliable and continuous operation, suitable for wet and dry grinding, easy maintenance and management.

Do you know!

- Factors affecting size reduction includes hardness, toughness, abrasiveness, stickiness and slipperiness of material, softening temperature, material structure, moisture content, bulk density, purity required, etc.

4.3 SIZE SEPARATION

Large pieces of material are usually estimated visually but difficulties arise only when powders are to be estimated. The aim of any estimation, including particle size separation, is either analytical or preparative. Size separation is a unit operation that involves the separation of a mixture of various size particles into two or more portions by means of sieving surfaces. Size separation is performed by processes known as sieving, sifting, segregation, etc. Granular mixtures separate according to particle size when shaken, with large particles rising; a phenomenon termed the 'Brazil-nut effect'. It is well known fact that differences in particle density affect size separation in mixtures of granular particles.

Particles of many kinds and various sizes have played an important role in development and production of dosage forms. If particles are spherical or cubical, it would be easy to characterize them. Unfortunately, most of the particles or granules in pharmaceuticals are of irregular size and shape. Therefore, various methods and techniques have been developed to characterize such particles. Particle size analysis is important in studying particle behavior in a medium during pharmaceutical applications. Size separation is based on physical differences between the particles such as size, shape and density.

(a) Definition:

Size separation is defined as a pharmaceutical process by which particles of different sizes are separated from a mixture to classify them into fractions based on size.

(b) Objectives:

Particles of many kinds and various sizes play an important role in performing specific function in development and use of dosage forms. If particles are spherical or cubical, it is easy to characterize them. Unfortunately, most of the particles employed in pharmaceuticals are of irregular size and shape. Therefore, it is desirable to develop methods and techniques to characterize particles of irregular size and shape, and this is the main objective of particle size separation. Apart from this other objectives of size separation are:

(1) To carry out grading of powders or granules to obtain fractions of narrow size range.

(2) To control size and avoid variations in the materials.

(3) To classify materials into different sizes for the desired application.

(4) To enhance performance, efficacy and stability of dosage forms.

(5) To judge uniformity in mixing materials and specify quality parameter for intermediate and finished dosage forms.

Do you know!

- Size separation is also known as sieving, sifting and screening.
- Mechanisms of size separation are oscillation, vibration and gyration.

4.3.1 Classification Powder According to IP

Standards for powders for pharmaceutical purposes are laid down principally in the Indian Pharmacopoeia which states that, the degree of coarseness or fineness of a powder is differentiated and expressed by the size of the mesh of the sieve through which the powder is able to pass. The IP specifies five grades of powder which are as under:

(a) Coarse Powder: A powder of which all the particles pass through a sieve with nominal mesh aperture of 1.7 mm (No. 10 sieve) and not more than 40% through a sieve with nominal mesh aperture of 355 µm (No. 44 sieve) is called coarse powder.

(b) Moderately Coarse Powder: A powder of which all the particles pass through a sieve with nominal mesh aperture of 710 µm (No. 22 sieve) and not more than 40% through a sieve with nominal mesh aperture of 250 µm (No. 60 sieve) is called moderately coarse powder.

(c) Moderately Fine Powder: If all the particles of a powder pass through a sieve with nominal mesh aperture of 355 µm (No. 44 sieve) and not more than 40% through a sieve with nominal mesh aperture of 180 µm (No. 85 sieve), it is moderately fine powder.

(d) Fine Powder: In case, all the particles pass through a sieve with a nominal mesh aperture of 180 µm (No. 85 sieve), it is called as fine powder,

(e) Very Fine Powder: If all the particles of the powder pass through a sieve with a nominal mesh aperture of 125 µm (No. 120 sieve), it is said to be a very fine powder.

4.3.2 Cyclone Separator

Cyclone separators provide a method of removing particulate matter from air or other gas streams at low cost and low maintenance. This separator is mainly used for the separation of solids from the liquids. It mainly consists of the tangential inlet to feed the materials inside the chamber. It has solid outlet and fluid outlet which separates fluid through one side and solids through the other side.

(a) Principle:

In the cyclone separator the centrifugal force is used to separate solids from the fluids (liquid or gas/air). The separation depends on the particles size as well as on the density of the particles. Hence, depending on the fluid velocity the cyclone separator can be used to separate all types of the particles to remove only coarse particles and allows fine particles to be carried through the fluid. It simply transforms the inertia force of gas particle flows to a centrifugal force by means of a vortex generated in the cyclone body. In a cyclone, the air containing particulate material is forced into along the tangential axis. A helical flow pattern is set up within the chamber. The centrifugal force causes the particles to migrate to the outside of the chamber. Here, they fall down to the bottom of the cyclone by gravity. The collected particles are allowed to exit out through an underflow pipe while the gas phase reverses its axial direction of flow and exits out through the vortex finder (gas outlet tube). The air moves-up the center of the cyclone and reaches the top.

(b) Construction:

Cyclone separators are a bit complicated in design with better removal efficiency. Cyclones are basically centrifugal separators. It consists of a cylindrical vessel referred to as the barrel with the conical base, Fig. 4.4. In the upper part of the vessel is fitted with a tangential inlet and a fluid outlet and at the base it is fitted with the solid outlet. Cyclones have no moving parts and available in many shapes and sizes. For example, cyclone separators of 1 to 2 cm diameter (for particle size analysis) to 5 m diameter (used after wet scrubbers), but the basic separation principle remains the same.

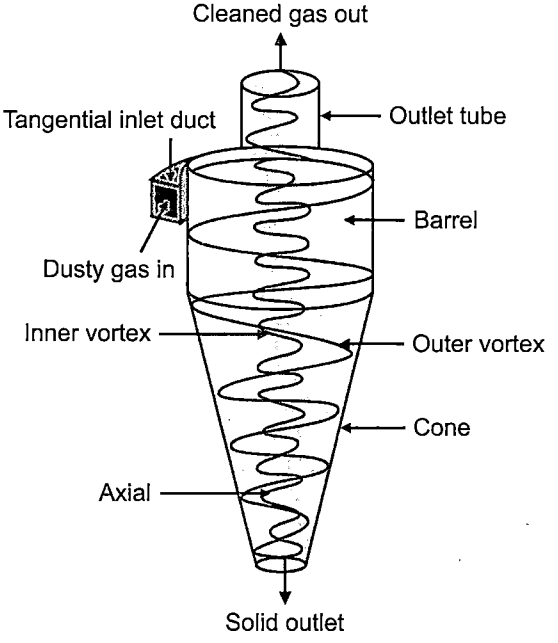


Fig. 4.4: A Schematic of Cyclone Separator

(c) Working:

The suspensions of a solid gas usually air is introduced tangentially at a very high velocity so that rotary movement takes place within the vessel. The fluid (gas) is removed from the central outlet at the top. The rotatory flow within the cyclone separator causes the particles to be acted on by centrifugal force. The solids are thrown out to the walls forming an outer vortex; thereafter it falls to the conical base and discharged out through solids outlet. The increasing air velocity in the outer vortex results in a centrifugal force on the particles separating them from the air stream. When the air reaches the bottom of the cone, it begins to flow radially inwards and out at the top as clean air/gas while the particulates fall into the dust collection chamber at the bottom of the cyclone.

The collection efficiency of cyclones varies as a function of density, particle size and cyclone design. Cyclone efficiency generally increases with increase in particle size and/or density, inlet duct velocity, cyclone body length, number of gas revolutions in the cyclone, ratio of cyclone body diameter to gas exit diameter, inlet dust loading, smoothness of the

cyclone inner wall etc. Similarly, cyclone efficiency decreases with increase gas viscosity, cyclone body diameter, gas exit diameter, gas inlet duct area, gas density, leakage of air into the dust outlet, etc.

(d) Applications:

A cyclone separator is most often used to separate "heavies" from a liquid mixture originating at a centrifugal pump or some other continuous source of pressurized liquid. A cyclone separator is most likely to be the right choice for processes where "lights" are the greater part of the mixture and where the "heavies" settle fairly easily. Cyclone separator may be used to separate solids from water. Its other applications include:

(1) Separation of suspensions of a solid in a gas or air or liquids.

(2) It is used in the production of drugs by spray or fluid bed drying.

(3) Used for separation of particles based upon size, specific gravity, porosity and concentration from solids, liquids and gases.

(4) It is mostly used for separation of fines from coarse granules.

(5) Cyclone is connected to the extraction line of a tablet press, intercepting waste powder before it reaches the central extraction system.

(6) It can be used in air-handling systems to produce particle free clean air.

4.3.3 Sieves

A sieve, also called sifter, is a device used for separating wanted elements from unwanted material or for characterizing the particle size distribution of a sample. It is made-up of using a woven sieve such as a mesh or net or metal. A sieve has very small holes. The sieving process is comparatively inexpensive, simple in concept and easy to perform. Coarse particles are separated or broken-up by grinding against one-another and sieve openings. Sieves are the most commonly used device for particle size analysis. Depending upon the types of particles to be separated sieves with different types of holes is used. Sieving plays an important role in pharmaceutical industries where they are used to prevent the contamination of the product by foreign bodies. The design of the industrial sieve is of primary importance.

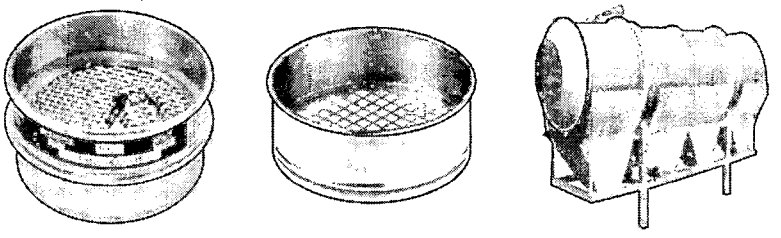
(a) Construction:

Based upon application specially designed sieves, for example, electroformed sieves, perforated plate sieves, sonic sifters, air jet sieves, wet wash sieves, etc., are used. Generally pharmaceutical sieves are made up of stainless steel, brass, bronze, etc., and are not coated with any material to avoid wear and tear as well as contamination in the products. Sieves for pharmaceutical use are non-reactive and resistant to corrosion. The most common choice of material for sieves is iron because it is cheap but has limitation for its use for its inherent corrosion and contamination properties. This can be avoided by coating iron surfaces with galvanizing agent. Stainless steel, brass and phosphorus bronze due to their corrosion resistant, good strength and non-contaminating qualities are preferred as an alternative to

iron. Even non-metals such as nylon and terylene are used if contamination is to be avoided. Sieves with different type of holes *viz.* size and shapes made in plates as perforations can also be used as separating devices. Sieves made-up of woven cloth made of cotton, nylon or silk are used if fine powders are to be separated.

(b) Types of Sieves:

Pharmaceutical sieves are extensively used for size separations from 300 mm down to around 38 μm. The efficiency of sieving decreases rapidly with fineness. Dry sieving is used for material above about 5 mm in size and wet sieving is common in use down to 250 μm but is possible to about 40 μm. In its simplest form, a sieve is a surface having many apertures (holes), usually with uniform dimensions. Particles presented to that surface either pass through or retained, according to whether the particles are smaller or larger than the dimension of the apertures. There are numerous different types of industrial sieves available, Fig. 4.5. Sieves can be classified based on design such as wire sieves, perforated sieves and horizontal sieves, trommels, roller sieves, flip-flow sieves, circular sieves, linear sieves etc. or based on mechanism of sieving such as vibrating sieves, static sieves, inclined or circular motion sieves, horizontal low-head, banana sieves, rotary scrubbers, etc.



(a) Wire sieve (b) Perforated sieve (c) Horizontal sieve

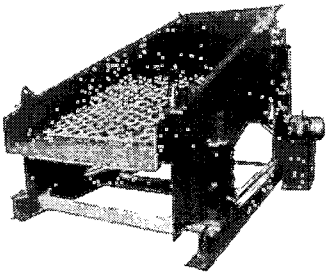
Fig. 4.5: Sieves Commonly Used in Pharmaceutical Processing

(i) Vibrating sieves: Vibrating sieves have a rectangular sieving surface for feed and oversize discharge at opposite ends. They are used in a variety of sizing, grading, scalping, dewatering, wet sieving, and washing applications. Sieves are vibrated in order to throw particles off the sieving surface so that they can again be presented to the sieve and to convey the particles along the sieve. Vibrating motion is produced with amplitude of 1.5–5 mm and operating in a range of 700–1000 r.p.m. The right type of vibration also induces stratification of the feed material, which allows the finer particles to move through the layer of particles to the sieve surface while causing larger particles to rise to the top. Vibrating sieves can be arranged with more than one sieve deck. On multiple-deck systems, the feed is introduced to the top coarse sieve, the undersize falling through to the lower sieve decks, thus producing a range of sized fractions from a single sieving.

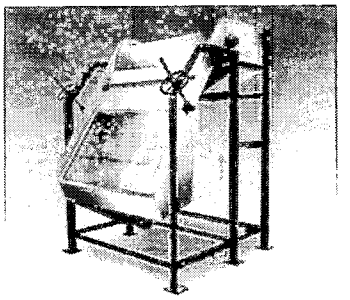
(ii) Inclined or circular motion sieves: A vertical circular or elliptical vibration is induced mechanically by the rotation of unbalanced weights or flywheels attached usually to a single drive shaft. The amplitude of throw can be adjusted by adding or removing weight elements bolted to the flywheels. The rotation direction can be contra flow or in-flow. Contra flow slows the material flow more and permits more efficient separation, whereas in-

flow permits a greater throughput. Single-shaft sieves is installed on a slope, usually between 15° and 28° angle to permit flow of material along the sieve.

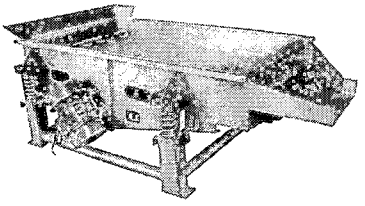
(a) Vibrating sieve



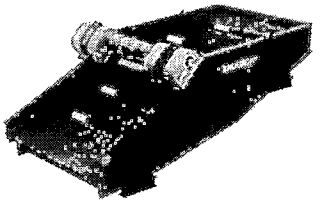
(b) Inclined sieve



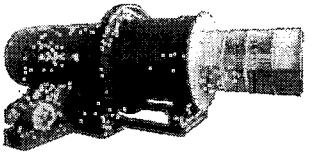
(c) Static sieve



(d) Horizontal low-head sieve



(e) Banana or multislope sieve



(f) Rotary scrubbers

Fig. 4.6: Types of Industrial Sieves

(iii) Static sieves: These sieves continuously remove solid materials from wastewater streams at ultra-high rates using zero energy and the cross-flow static sieve continuously removes oversize particles from coarse, free-flowing, dry bulk solids at higher rates. They have fixed-slope and are heavy-duty having permanent bar screen with apertures from 6mm to 76 mm. Very coarse material is usually sieved on an inclined sieve called grizzly sieve. Grizzlies are characterized by parallel steel bars or rails set at a fixed distance apart and installed in line with the flow of ore.

(iv) Horizontal low-head sieves: These sieves have a horizontal or near-horizontal sieving surface and therefore need less headroom than inclined sieves. Horizontal sieves are vibrated with a linear or an elliptical vibration. The accuracy of particle sizing on these sieves is superior to that on inclined sieves; however, because gravity does not assist the transport of material along the sieve, they have lower capacity than inclined sieves. These sieves are used in sizing applications where sieving efficiency is critical.

(v) Banana or multislope sieves: These sieves become widely used for large sample sizing applications where both efficiency and capacity are important. Banana sieves typically have a variable slope of around 40–30° at the feed end of the sieve, reducing to around 0–15° at the discharge end in increments of 3.5–5°. The steep sections of the sieve cause the feed material to flow rapidly at the feed end of the sieve. The resulting thin bed of particles stratifies more quickly and therefore has a faster sieving rate for the very fine material than would be possible on a slower moving thick bed. Toward the discharge end of the sieve, the slope decreases to slow down the remaining material, enabling more efficient sieving of the near-size material.

(vi) Rotary scrubbers: A rotary scrubber is a cylindrical drum with internal lifters, typically supported by trunnion rollers at either end. These are high-capacity, high-retention time machines primarily used to remove water-soluble clays, deleterious materials, and coatings from a wide variety of hard rock and ore. Rotary scrubber designs include the solid shell and combination scrubber sieves and are available in a variety of diameters and lengths. Drive transmission choices include chain and sprocket, gear and pinion, or pedestal mount hydraulic motor. These sieves are uncommon in pharmaceutical applications.

(c) Applications:

(1) Sieves are used for particle size analysis of variety of dry and wet materials.

(2) These are used for size separation of coarse materials down to 150 μm.

(3) These used in pharmaceutical production to determine product quality and integrity.

(4) Sieves are used to ensure that ingredients and finished products are quality assured during production and before use or dispatch.

4.3.4 Standards of Sieves

Sieving is the separation of fine material from coarse material by means of a meshed or perforated surface. The technique was used since early Egyptian days as a way to size grains. These early sieves were made of woven reeds and grasses. Today the sieve test is the technique used most often for analyzing particle-size distribution. Although at first look the sieving process appears to be elementary, in practice, there is a science and art involved in producing reliable and consistent results.

Table 4.1: Standards for Sieves

Standard	Description
Sieve Number	The sieve number is number of meshes in length of 2.54 cm in each transverse direction parallel to the wires. Mesh is arranged in multiple configurations. Mesh can be a square pattern, long-slotted rectangular pattern, circular pattern, or diamond pattern.
Nominal size of aperture	This term is the distance between the wires. It represents the length of side of a square aperture. The relation between Nominal size of aperture and size in mm or micrometer is given in I.P.
Nominal diameter of the wire	A wire with specific diameter is used for particular sieve. Diameter of wires gives strength to avoid distortion in the meshes.
Approximate percent sieving area	This standard expresses the area of meshes in percent to total area of sieve. The approximate sieving area range from 35 to 40% of sieve area. This area is suitable to give enough strength to sieve while sieving. It depends on diameter of wire.
Aperture tolerance average percent	During making or use some variations in the aperture size takes place that are expressed as aperture tolerance average percent. It is small for coarse sieves while greater for small size sieves.

Table 4.2: Specifications for Wire and Aperture Size of Sieves as Per I.P.

Sieve No.	Nominal aperture size (mm)	Nominal wire diameter (mm)	Standard wire gauge	Approximate screen area (%)	Average aperture tolerance (%)
6	3.812	1.422	17.0	44	3.2
8	2.057	1.118	18.5	42	3.3
10	1.676	0.864	20.5	44	3.3
22	0.699	0.457	26.0	36	4.0
25	0.599	0.417	27.0	35	4.2
30	0.500	0.345	29.0	35	4.4
36	0.422	0.284	31.5	36	4.9
44	0.353	0.224	34.5	38	4.8
60	0.251	0.173	37.0	35	5.3
85	0.178	0.122	40.0	35	5.9
100	0.152	0.102	42.0	35	6.2
200	0.076	0.051	47.0	36	8.2

Sieves used in pharmaceutical industry must comply with the standards given in Pharmacopoeia, Table 4.1. To better understand sieving, there are several areas of sieve specifications that should be explained and some of them are given in Table 4.2. The different international sieve standards and the corresponding sieve types are presented in Table 4.3. There are several sieve aperture progression ratios commonly available depending on the different international standards. ASTM Test Sieves come in several diameters such as 3" (76 mm), 6" (152 mm), 8" (203 mm), 10" (254 mm), 12" (305 mm), and 18" (457 mm) and full or half-height frames with different sieve sizes for a wide range of particle sizes. Each sieve has a specific number that denotes the number of meshes in a length of 2.54 cm (≈1 inch).

In the USA, a progression ratio of $2^{0.5}$ is used. This ratio corresponds to successive particle groups of 2:1 particle surface ratio. The progression rate of $2^{1/3}$ ($10^{0.1}$) which has been adopted by the French corresponds to successive particle groups of 2:1 particle volume ratio. The progression ratios of $10^{0.1}$ and $10^{0.05}$ are recommended for narrow size distributions.

Table 4.3: International Sieve Standards

Country	Standard	Sieve type
Great Britain	BS 410	Woven wire
USA	ASTM E11	Woven wire
	ASTM E161-607	Micromesh (electroformed)
Germany	DIN 4188	Woven wire
	DIN 4187	Perforated plate
France	AFNOR NFX 11-501	Woven wire
International	ISO R565 1972(E)	Woven wire, Perforated plate

4.4 MIXING

In pharmaceutical processing mixing involves certain heterogeneous components to be manipulated with the intent to make them more homogeneous. The mixing is defined as a process that results in randomization of dissimilar particles within a system. Mixing may be performed between any two phases ranging from mobile liquids to viscous liquids to semi-solids and solids. It is performed to allow heat and/or mass transfer to occur between one or more streams, components or phases. In modern industrial processing involves chemical reactors as mixers.

(a) Definition:

Mixing is defined as an operation in which two or more components in a separate roughly mixed condition are treated so that each particle lies as nearly as possible in contact with a particle of each of the other ingredient.

(b) Objectives:

The aim of mixing is to ensure that there is uniformity of composition between the mixed ingredients that represent overall composition of the mixture. The primary objective of mixing is to make homogeneous product using the minimum amount of energy and time. The other objectives of mixing are as follows:

(1) To produce single physical mixture: This may be simply the production of a blend of two or more miscible liquids or semisolids or two or more uniformly divided solids. In pharmaceutical practice, the degree of mixing is of high order as many such mixtures are dilutions of active substances and must be in accurate amount for dose uniformity in dosage forms.

(2) To produce physical change: Mixing can be performed to produce physical as well as chemical change, for example, solution of a soluble substance. In such cases a lower efficiency of mixing is often acceptable because mixing merely accelerates a dissolution and diffusion process that could occur by simply agitation.

(3) **To produce stable dispersion:** Mixing is also aimed to include dispersion of two immiscible liquids to form an emulsion or dispersion of a solid in liquid to give a suspension or paste. Usually good mixing is required to ensure stability and effectiveness.

(4) **To promote chemical reaction:** Mixing encourages and controls a chemical reaction. Mixing ensures uniform product such as reactions where accurate adjustment to pH is required and the degree of mixing decides the possibility of reaction.

Mixing fulfills many objectives beyond simple combination of raw ingredients. These include reducing particle size, manipulating rheology, dissolving components, facilitating heat transfer, etc. So even within a single pharmaceutical product line, it is a common practice to employ a number of different style mixers to process raw ingredients, handle intermediates and prepare finished products.

4.4.1 Double Cone Blender

Mixing is a common process step in the manufacture of products for industries such as healthcare, food, chemical, cosmetics and detergents. The double cone blender (DCB) is used to produce homogeneous solid-solid mixture. DCB is an efficient and versatile mixer blender providing good product rolling and cross mixing. It performs mixing, uniform blending and de-agglomeration functions. The conical shape at both ends enables uniform mixing and easy discharge. Powder loading and discharge are through separate opening.

(a) Principle:

Double cone blenders are most often used to dry blending of free solids. The solids being blended in these blenders can vary in bulk density and percentage of the total mixture. The materials being blended are constantly intermixed as double cone rotates. Normal blending cycle time is 10 min and can be more or less depending upon the complexity of material being mixed.

(b) Construction:

Double cone blender is made out of stainless steel. The main body of the blender consists of two cone-shaped sections welded at their bases to a central cylindrical section. The axis of rotation is perpendicular to the cone axis and passes through the cylindrical section. The driving motor is located at one of the two lateral supports holding the blender body. All welding are done by Argon Arc Process. This is totally mirror polished from inside and outside. Unit is mounted on mild steel / stainless steel stand fitted with ball bearings. It is available in capacity of 20 L to 3000 L. The conical shape at both ends enables uniform mixing and easy discharge. The cone is statically balanced which protects the gear box and motor from any excessive load. The suitable size of butterfly valve at one end of the cone is provided for material discharge and hole with openable cover is provided at other end of the cone for material charging and cleaning. The driving arrangement consists of a motor and stainless steel baffles inside the blender. Ancillary provisions include facility for

incorporation of a liquid spray system to introduce liquids in spray form during the process. The unit can be equipped with an automated loading system for introducing powders and granules into the blender body by means of a vacuum unit with self-cleaning hoses.

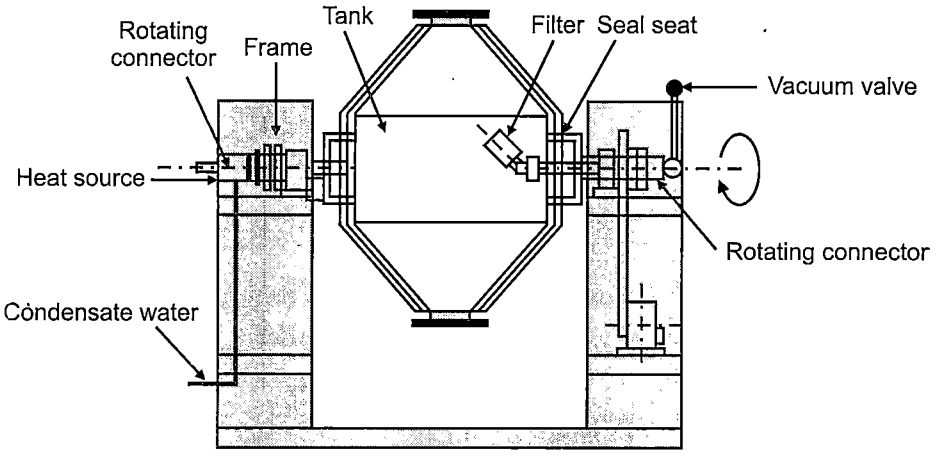


Fig. 4.7: A Double Cone Blender

(c) Working:

Powdery or granular materials are fed into the double cone containers using vacuum intake system or manual feeding. The continuous rotation of the containers makes the material to move in a complex and forceful manner to achieve uniform mixing. The conical shape at both ends contributes to uniform mixing and easy discharge. Depending upon the characteristic of the material, paddle type baffles can be provided on the shaft for better mixing, uniform blending and de-agglomeration. Dust free bin charging system ensures minimum material handling. The solids are introduced into the blender through the loading aperture. The mixing takes place axially, as a result of the powder bed moves through the different sections. Mixing is thorough but it depends on the rotating speed. The mixture is discharged through a hermetically closing butterfly valve which is operated manually or automatically. The blender provides efficient mixing actions when loaded at 50% of its volume. The effective volume for optimum homogeneity is 35-70% of gross volume.

(d) Applications:

(1) The DCB is useful for mixing dry powder and granules for tablet and capsules.

(2) It can be suitable for dry powder to wet mixing.

(3) It is used for dry granule mixing to increase the batch size at bulk lubrication stage.

(4) It can be used for mixing food, chemical, cosmetic product intermediates.

(5) It is used in mixing highly flowable powdery and granular materials, with superior mixing quality.

(6) It is suitable for mixing of process intermediate powder materials whose specific gravity is under 7 g/cm^3 that has certain fluidity with the liquid content under 10%.

4.4.2 Turbine Mixer

Turbine mixer is another type of process agitator. They are used as an alternative to propellers for mixing low viscosity liquids and typically for the effective mixing of medium viscosity liquids. The velocity of mixing using turbine systems is low compared to propellers.

(a) Principle:

Turbine mixer agitators can create a turbulent movement of the fluids due to the combination of centrifugal and rotational motion. This combined motion causes effective mixing of low to medium viscosity fluids.

(b) Construction:

A turbine consists of a circular disc to which a number of short blades are attached. There is a wide range of turbine designs, Fig. 4.8. The blades may be straight, pitched, curved or disk type. The diameter of the turbine ranges from 30-50% of the diameter of the mixer vessel. Turbine rotates at a lower speed usually 50 – 200 r.p.m. Flat blade turbines produce radial and tangential flow but as the speed increases radial flow dominates. Pitched blade turbine produces axial flow. Near the impeller zone of rapid currents, high turbulence and intense shear is observed. Shear produced by turbines can be further enhanced using a diffuser ring. The diffuser ring is a stationary perforated ring which surrounds the turbine.

(c) Working:

A mixer is filled through an opening at its top. Usually, it is a pan or drum within which mixing blades revolve about the vertical axis. The variable speed drills with turbine mixer whip air into the mixture of materials. The air in mixture yield bubbles contributing mixing. The top entry turbine mixer is fitted with various impellers and turbines to suit heat and mass transfer in solids, suspensions and liquids. This type of mixer does not damage product. Top entry high shear causes uniform emulsification and homogenization. The mixing blades revolve about the vertical axis.

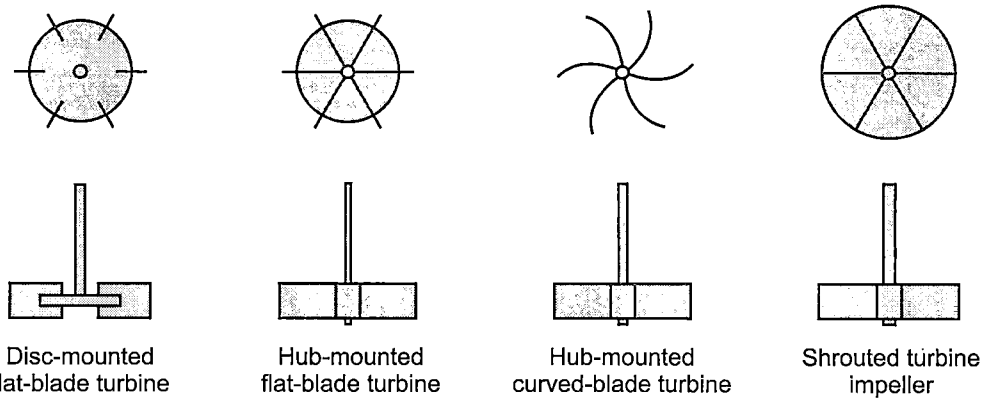


Fig. 4.8: Various Types of Turbines

(d) Applications:

(1) Highly used in chemical reactions and extraction operations, for example, liquid and gas reactions.

(2) Used in preparing emulsions, suspensions and syrups.

(3) Used to mix high viscosity liquids, semisolids and paste.

4.4.3 Triple Roller Mill

Roller mill is a form of compression mill that uses a single, double, or triple cylindrical heavy wheel mounted horizontally and rotated about their long axis either in opposing pairs or against flat plates, to crush or grind various materials. A triple roll mill is effective mixing equipment used for squeezing (compression) and homogenizing of pastes. It is user friendly machine that consists of corrosion resistant contact parts. This mill is used mostly for dispersion, but does some grinding as well. It uses three rollers of different speeds and directions to cause the sheer force between them to disperse and grind particles.

(a) Principle:

A three roll mill is a machine tool that uses the shear force created by three horizontally positioned rolls rotating at opposite directions and different speeds relative to each other to mix, refine, disperse, or homogenize viscous materials fed into it. The grinding effect is achieved by mutually pressing the surfaces of the three horizontal rollers and rubbing at different speeds.

(b) Construction:

This mill has three rollers mounted on an iron frame installed horizontally or slightly tilted. The roller material is centrifugally cast from chilled-hard alloy cast iron. The gaps between the rollers are adjustable independently from each other via a single knurled screw, which is scaled from 0 to 4. Rollers are fitted in such a way that they come in close contact with each other and rotate at different speeds. The gap between rollers is between 0.05 mm - 0.3 mm. Rollers can be hollow and cooled by water. The outer rollers are spring-supported. The centre roll is fixed and feeding and discharge rolls are movable mechanically. The driving gears are made of wear resistant castings. The feeding hopper cheeks are made out of fine quality gun metal and sit on the roll surface. It has adjustable hopper cheeks to accommodate smaller and larger batches. The discharge chute is chrome plated and is fitted with an adjustable scraper knife and can be pressed, released, cleaned or replaced easily.

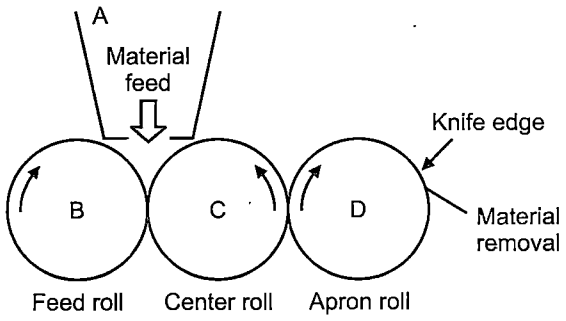


Fig. 4.9: Triple Roller Mill

(c) Working:

The rolling action in this mill is generated by the contra rolling motion of three robust rollers. Since the three rollers rotate in different directions, a good grinding action is produced. The feed material is added from hopper between the middle roll and the back roll. The material that come, in-between the rollers is crushed and reduced in particle size. The reduction in particle size depends on the gap between the rollers and difference in their speeds. For example, Fig. 4.9, the feed material is allowed to pass through hopper A, in-between the rollers B and C where it is reduced in size. Then the material is passed between the rollers C and D where it is further reduced in size and a smooth mixture is obtained. The gap between rollers C and D is usually less than the gap between B and C. After passing the material between rollers C and D the smoothened material is continuously removed from roller D by means of scraper, from where it is collected in a receiver.

(d) Applications:

(1) To disperse material within a semi-viscous material such as cream.

(2) Used in the homogenization during preparation of ointments, creams, pastes, doughs and other viscous preparations.

(3) It is used for mixing pharmaceutical, herbal and alternative medicine, chemicals and fine chemicals, food, agriculture, cosmetics and detergents, pigments, etc.

(4) It can also be used in mixing of coating compositions, composites, adhesives, sealants and foods.

4.4.4 Silverson Mixer

Silverson mixer has been the leader in high shear mixing for over 60 years. This mixer operates at high speeds up to 8000 r.p.m.

(a) Principle:

The principle of Silverson mixer is based upon shearing force. It produces intense shearing forces and turbulence by use of high speed rotors. Circulation of material takes place through the head by the suction produced in the inlet at the bottom of the head. Circulation of the material ensures rapid breakdown of the dispersed liquid into smaller globules or fines.

(b) Construction:

It consists of long supporting columns and a central portion. Central portion consists of a shaft which is connected to motor at one end and other to the head. Head carries turbine blades. The mixer body is raised or lowered electrically. It stops automatically at the higher and lower limits of movement. Blades are surrounded by a mesh, which is further enclosed by a cover having openings. It has several accessories with the mixer, which can be interchanged depending on mixing conditions required and material being mixed. It consists of following accessories:

(1) **General purpose disintegrating head:** Suitable for general mixing or disintegration of solids.

(2) **Square hole high shear screen:** High shear screen suitable for emulsion and fine colloid suspension preparation.

(3) **Emulsor screen:** Lower shear screen suitable for liquid/liquid and emulsion preparations.

(4) **Axial flow head:** Used in addition to one of the above screens to force liquid flow upwards This can reduce aeration or help maintain large suspensions, but high mixing speeds can cause liquid to be ejected from the mixing vessel.

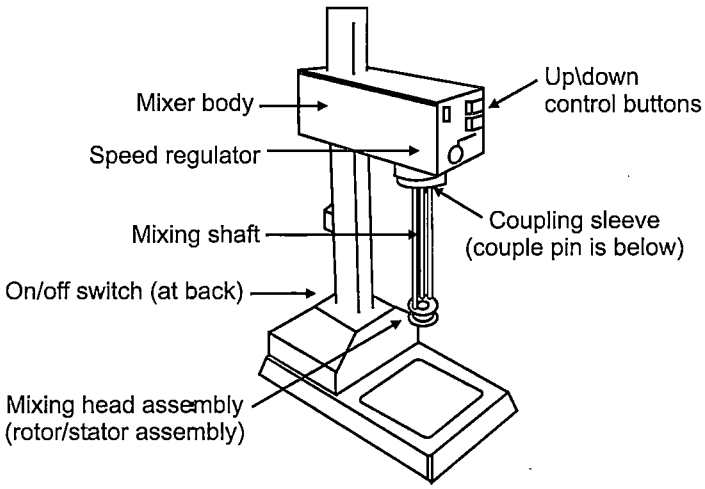


Fig. 4.10: Silverson High Shear Mixer

(c) Working:

The precision-machined Silverson work head generates exceptionally high shear rates in a three stage process that rapidly homogenizes the product to the required uniformity.

(1) The high-speed rotation of the rotor blades within the mixing work head exerts a powerful suction, drawing liquid and solid materials into the rotor/stator assembly.

(2) The centrifugal force drives the material towards the periphery of the work head where they are subjected to a milling action in the clearance between the ends of the rotor blades and the inner wall of the stator.

(3) This is followed by intense hydraulic shear as the materials are forced at high velocity out through the perforations in the stator, then through the machine outlet and along the pipe work. At the same time, fresh materials are continually drawn into the work head, maintaining the mixing and pumping cycle.

(d) Applications:

(1) It is used to mix, emulsify, homogenize, solubilize, suspend, disperse and disintegrate solids.

(2) It is used for homogenization of vast variety of products such as creams and ointments, lotions, sauces and flavour emulsions.

(3) Silverson mixers can be used to disintegrate matter of animal, vegetable, mineral or synthetic origin in a single operation.

(4) It is also used in rapidly gelling, solubilizing and dispersing gums, alginates, carbopol, etc., resulting in an agglomerate-free solution within minutes.

4.4.5 Homogenizer

Homogenization is a process in which coarse globules in emulsion are converted into smaller globules of uniform composition, so that each measured dose has the same composition. Homogenizers are used for the preparation of biphasic systems like suspensions and conversion of coarse emulsion to colloidal emulsion.

(a) Principle:

Homogenization is the process of converting non-uniform mixture to a colloidal state or a uniform mixture. It is done by reducing particle size of mixtures or uniform dispersion of the mixtures making the product homogenous. The principle of homogenizer is that when large globules in coarse emulsion are passed under high pressures through a narrow orifice are broken into smaller globules having a greater degree of uniformity and stability.

(b) Construction:

(i) Simple Homogenizer: It consists of a pump that raises the pressure of the dispersion to a range of 500-5000 psi and an orifice through which the fluid strikes upon the homogenizing valve. The homogenizing valve is held on valve seat by strong spring. As the pressure increases some of the dispersion escapes between valve and valve seat, and instantly pressure is released which subjects the product to intense turbulence and hydraulic shear.

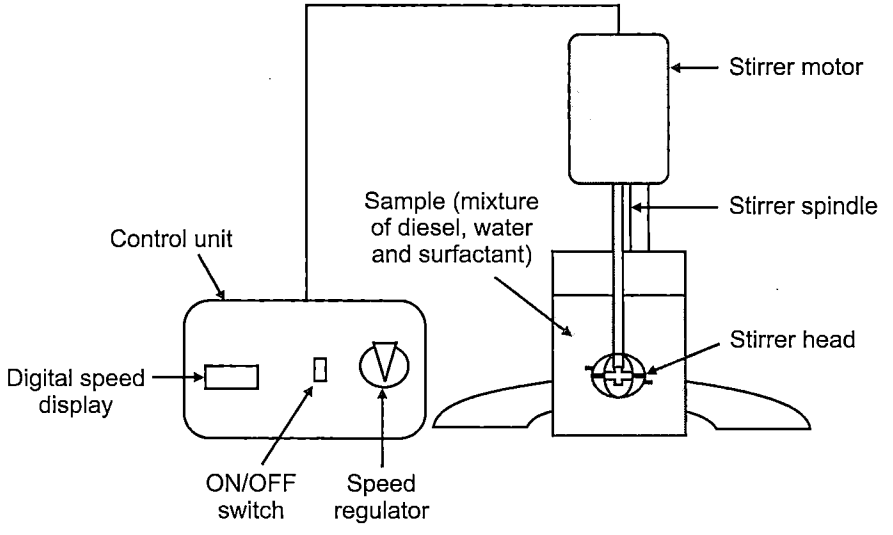


Fig. 4.11: Simple Homogenizer

(ii) Modified Turbines: It consists of turbine and stator at a certain distance in the mixer. The rotation of turbines at very high speed creates a pressure difference and reduces the particle size. The particles and fluids pass through the stator and turbines which produces mechanical forces (cavitation, turbulence, impact and shear) to obtain uniform or homogenized mixture.

(iii) High Pressure Homogenizer: High-pressure homogenizer (HPH) forces a stream of liquid sample through a system which subjects it to number of forces which is intended to homogenize the sample and/or reduce the particle sizes of any components within it. It consists of high pressure pump fitted to stainless steel fluid tank. HPH includes the types of pressure pumps and piston pumps, geometry and design of valves, O rings, and impact rings. As a result of the application of mechanical forces, the liquid that flows out of the homogenizer has a much smaller particle size.

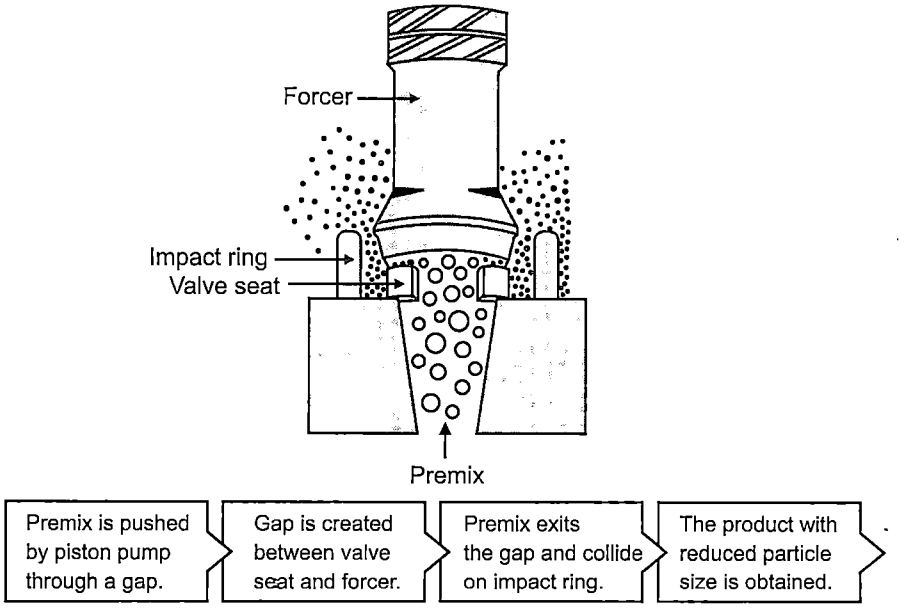

Forcer
Impact ring
Valve seat
Premix
Premix is pushed by piston pump through a gap.
Gap is created between valve seat and forcer.
Premix exits the gap and collide on impact ring.
The product with reduced particle size is obtained.

Fig. 4.12: High Pressure Homogenizer

(iv) Ultrasonic Homogenizer: Ultrasonic homogenizer is another example of pressure homogenizer where ultrasonic waves (frequency above 20000 Hz) are generated for mixing or uniform dispersion of the mixtures. The ultrasonic waves produce shear effect responsible for size reduction and homogenization. It is used primarily for emulsification. When a liquid is subjected to ultrasonic vibrations alternate regions of compression and rarefaction are produced in the liquid. Cavities are formed in the regions of rarefaction which subsequently collapse in the regions of compression which results great forces for emulsification. It consists of a pump driven by a motor. It is connected to inlet tube and an outlet tube. Head consists of a flat jet for liquid inlet. Facing the jet, a thin blade is present which vibrates at its natural frequency.

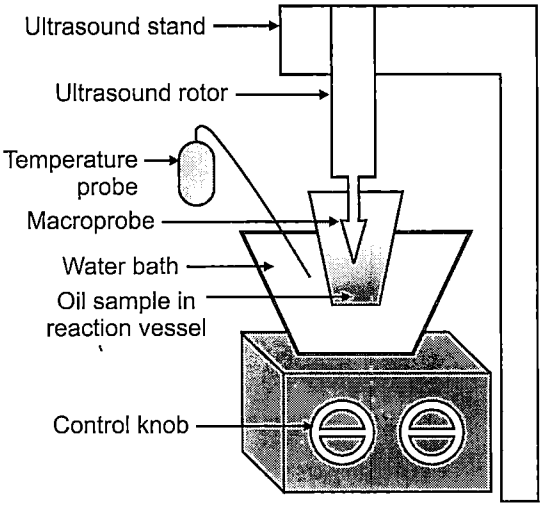


Fig. 4.13: Ultrasonic Homogenizer

(b) Working:

Homogenizer mainly works by agitating the liquid that is to be homogenized. Agitation can be done by using a mechanical arrangement which pumps the liquid through an orifice plate. Agitation can also be done by an acoustic medium which uses ultrasonic frequency to agitate a surface over which the liquid is pumped.

Applications:

(1) Homogenizers are used in synthesis of essential drug components such as tissue, plant, food, soil, and many others by homogenizing them.

(2) These are used in preparation of pharmaceutical emulsions, suspensions and semisolid and cosmetic products.

(3) Used to increase bioavailability and chemical stability and enhance physical appearance of dosage forms by reducing particle size of solids.

4.5 FILTRATION

In pharmaceutical material processing removal of solids takes place by a number of mechanisms that include straining, flocculation, coagulation, sedimentation and surface capture. Filters can be categorized by the main method of capture, for example, exclusion of particles at the surface of the filter media (straining), or deposition within the media (in-depth filtration). Filtration is a common operation widely employed in the production of sterile products, bulk drugs, and in liquid oral formulation. The suspension of solid and liquid to be filtered is known as the slurry. The porous medium used to retain the solids is described as the filter medium; the accumulation of solids on the filter is referred to as the filter cake, while the clear liquid passing through the filter is the filtrate. The pores of the filter medium are smaller than the size of particles to be separated.

(a) Definition:

Filtration is a unique unit mechanical or physical process of separating suspended and colloidal particles from fluids (liquids or gases) by interposing a medium through which only the fluid can pass.

(b) Objectives:

The main learning objective of filtration is to separate solids from liquid or gas medium. The other objectives include:

(1) To eliminate the contaminant particles so as to recover dispersing fluid.

(2) To recover solid particles by eliminating the dispersing fluid.

(3) To produce high-quality solvents and solids.

(4) To purify air and pharmaceutically useful gases by removing particulate matter.

(5) To sterilize thermolabile parentral products.

4.5.1 Theory of Filtration

The flow of any liquid through any porous medium offers a resistance to its flow. The rate of filtration in such cases is expressed as:

$$\text{Filtration rate} = \frac{\text{Driving force}}{\text{Resistance by filter medium}} \quad \ldots (4.1)$$

The net driving force in filtration is pressure above the medium minus pressure below the medium. The resistance offered by filter medium is not constant over the period of filtration as it goes on increasing with time due to particle deposition on filter medium. Rate is expressed as volume of filtrate per unit time (dv/dt). Depending on dispersing (fluid) medium, filtration theory is divided in two parts.

(a) Gas Filtration Theory:

Gas filtration includes filtration of aerosol and lyosol. Membrane filters and nucleopore filters are used for gas filtration which works on the following mechanisms:

(1) Diffusion deposition: In this mechanism the trajectories of individual small particles do not coincide with the streamlines of the fluid because of Brownian motion. With decreasing particle size, the intensity of Brownian motion increases and thus as a consequence, the intensity of diffusion deposition also increases.

(2) Direct interception: This mechanism involves finite size particles. These particles are intercepted as they approach the collecting surface to a distance equal to its radius.

(3) Inertial deposition: The presence of particles in the flowing fluid results in a curvature of the streamlines in the neighborhood of the body. Because of their inertia, the individual particles do not follow the curved streamlines but are projected against the body and may deposit there. It is obvious that the intensity of this mechanism increases with increasing particle size and velocity of flow.

(4) Gravitational deposition: Individual particles have a certain sedimentation velocity due to gravity. As a consequence, the particles deviate from the streamlines of the fluid and, owing to this deviation; the particles may touch a fiber.

(5) Electrostatic deposition: Both the particles and the fibers in the filter may carry electric charges. Deposition of particles on the fibers may take place because of the forces acting between charges or induced forces.

(b) Liquid Filtration Theory:

The term filtration covers all processes in which a liquid containing suspended solid is freed of some or the entire solid when the suspension is drawn through a porous medium. Filtration is of two types namely; 'Cake filtration' where the proportion of solids in suspension is large and most of the particles are collected in the filter cake which can subsequently be detached from the medium and 'Deep bed filtration' where the proportion of solids is very small. For example, in water filtration, the particles are often considered as smaller than the pores of the filter medium and penetrate at a considerable depth for being captured.

Kozeny-Carman Equation:

In the filtration as particles forming the cake are small and the flow through bed is slow, streamline conditions are almost invariably obtained, Fig. 4.14.

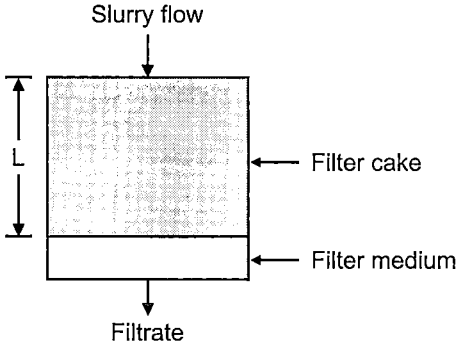


Fig. 4.14: Schematic of Filtration

At any instant it may be explained by Kozeny-Carman equation as:

$$U = \frac{1}{A}\frac{dv}{dt} = \frac{\Delta P}{r\mu\,(l + L)} \quad \ldots (4.2)$$

Where, U is flow rate, A is filter area, v is total volume of filtrate delivered, t is filtration time, ΔP is pressure drop across cake and medium, r is specific cake resistance, μ is filtrate viscosity, l is cake thickness and L is thickness of cake equivalent to medium resistance.

Kozeny-Carman equation has certain limitations that it does not take into account the fact that depth of the granular bed is lesser than the actual path travelled by the fluid. The actual path is not straight throughout the bed, but it is sinuous or tortuous.

Poiseuille's law:

Poiseuille's law considers that filtration is similar to the streamline flow of a liquid under pressure through capillaries.

$$\frac{1}{dv}\frac{A}{dt} = \frac{\Delta P}{\mu (Rm + Rc)} \quad \ldots (4.3)$$

$$\text{Cake resistance (Rm)} = \frac{\sigma W}{A} \quad \ldots (4.4)$$

$$\text{Specific cake resistance } (\sigma) = \sigma' \Delta P^{s} \quad \ldots (4.5)$$

The filter resistance is much less than the cake resistance i.e. Rc << Rm. Therefore, on rearranging equation (4.1):

$$\frac{1}{dv}\frac{A}{dt} = \frac{\Delta P}{\mu (\sigma' DP^{S} \times WA)} \quad \ldots (4.6)$$

Where, v is filtrate volume, A is filter area, t is time, ΔP is pressure driving force, μ is broth viscosity, W is mass of filter, R is resistance, σ is specific cake resistance and S is compressibility factor.

Darcy's Equation:

When using Poiseulle equation for filtration it is considered that capillaries in filter medium are highly irregular and non-uniform. In order to approximate the flow rate the height of cake is taken as length of capillaries and a correction factors is introduced for the radius of capillaries. This makes rate more simplified and is expressed as;

$$U = \frac{KA\,\Delta P}{\eta L} \quad \ldots (4.7)$$

Where, U is flow rate, K is permeability coefficient, A is surface area of filter medium, ΔP is pressure difference across the filter, r is capillary radius in filter bed, L is capillary length.

The permeability coefficient (K) depends on porosity, specific surface area and compressibility of cake. This coefficient is may be defined as the flow rate of a liquid of unit viscosity across unit area of cake with unit thickness under the unit pressure gradient.

4.5.2 Membrane Filter

A membrane is a thin layer of semi-permeable material that separates substances when a driving force is applied across the membrane. It works on the principle of physical separation. These are used for removal of bacteria, micro-organisms, particulates, and natural organic material, which can impart colour, tastes, and odours to water and react with disinfectants to form disinfection byproducts. Advancements are made in membrane production and module design with the view to reduce capital and operating costs. The membrane processes includes microfiltration, ultrafiltration, nanofiltration and reverse osmosis.

(a) Principle:

The principle is quite simple that the membrane acts as a very specific filter that allows water to flow through, while it catches suspended solids and other substances. Membrane filter uses the sieving mechanism of the microfiltration membrane, driven by pressure, to trap particles with a diameter between 0.1-1 μm, such as suspended solids, bacteria, some viruses, and large-sized colloids. Water flow through the membrane is not very fast, so in order to pass the required amount of water, the monomer area of the membrane device is large, and many thin membrane tubes are filled in a small space.

(b) Construction:

Membrane filters are plastic membranes based on cellulose acetate, cellulose nitrate or mixed cellulose esters with pore sizes in the micron or submicron range. They are very thin about 120 μ and must be handled carefully. They act like a sieve trapping particulate matter on their surface. Several grades of filters are available with pore sizes ranging from 0.010 ± 0.002 μ to 5.0 ± 1.2 μ. Type codes VF and SM are given by Millipore Filter Corp. for these two extreme ranges, respectively. Filters with pore sizes from 0.010 to 0.10 μ can remove virus particles from water or air. Filters with pore sizes from 0.30 to 0.65 μ are employed for removing bacteria. Filters with the larger pore sizes, viz. 0.8, 1.2 and 3.0 to 5.0 μ are employed, for example, in aerosol, radio activity and particle sizing applications.

Membrane filters are manufactured as flat sheet stock or as hollow fibers and formed into several different types of membrane modules. Module construction involves potting or sealing the membrane material into an assembly, such as with hollow-fiber module. These types of modules are designed for long-term use over the course of a number of years. Spiral-wound modules, Fig. 4.15, are manufactured for long-term use.

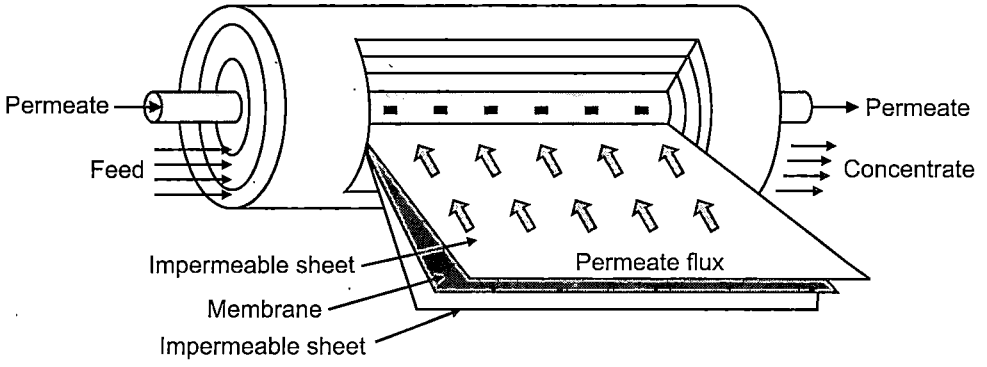


Fig. 4.15: Spiral Wound Membrane Filter

(c) Working:

The membrane separation process is based on the presence of semipermeable membranes. The principle is membrane acts as a very specific filter that will let water flow through, while it catches suspended solids and other substances. During use membrane filters are supported on a rigid base of perforated metal, plastic or coarse sintered glass. If the solution to be filtered contains a considerable quantity of suspended matter, preliminary

filtration through a suitable depth filter avoids clogging of the membrane filter during sterile filtration. They are brittle when dry and can be stored indefinitely in the dry state but are fairly tough when wet.

(d) Applications:

(1) Membrane filtration is used as an alternative to flocculation, sediment purification techniques, adsorption (sand filters and active carbon filters, ion exchangers), extraction and distillation.

(2) It is used in dehydration, concentration/separation of substances or the treatment of residual liquids.

(3) It is in concentration of dissolved or suspended solids, and for obtaining a rejected liquid that contains a very low concentration of dissolved solids.

(4) It allows the isolation and enumeration of micro-organisms.

(5) It is used in removal of ammonium ions from potable water.

(6) It can also be used in the manufacture of dairy ingredients such as milk, whey and clarified cheese brine.

(7) It is used in starch and sweetener industry to clarify corn syrups, concentrate rinse water from starch, the enrichment of dextrose, the depyrogenation of dextrose syrup, etc.

(8) It is used in the industrial production lines for enzymes in concentrating them prior to other processes.

4.5.3 Sintered Glass Filter

Sintered glass is a glass mesh used for filtration. It is available in different pieces of glassware. A suction funnel made of glass has its base made of very porous sintered glass. Sintered glass filters are more convenient to use than Buchner funnels because there is no filter paper to worry about, but they are harder to clean.

(a) Principle:

The liquid to be filtered is poured into the sintered glass funnel and drawn through the perforations by vacuum suction. These flasks are attached to vacuum pump to carry out filtration under reduced pressure to allow for the suction and collection of the filtrate.

(b) Construction:

Sintered glass filter available in different pore size are made of borosilicate glass. Borosilicate glass is finely powdered, sieved and particle of desired size are separated. It is then packed into a disc mould and heated to a temperature at which adhesion takes place between the particles to form porous structure, Fig. 4.16. The disc is then fused to a funnel of suitable shape and size. Sintered filters are also made up of stainless steel which has a greater mechanical strength. However, these steel filters are very much liable to attack by the solutions passing through them. The funnel with a sintered filter is numbered according to the pore size. Porosity of sintered glass is labeled by integers from 0 - 5 (viz. 0, 1, 2, 3, 4, 5) where 0 has a pore size of 160-250 μm and is considered coarse filtration, that is fluid will

pass through it quickly and some finer solids will pass through. Whereas, porosity 5 has a pore size of 4-10 μm through which only liquids will drop through.

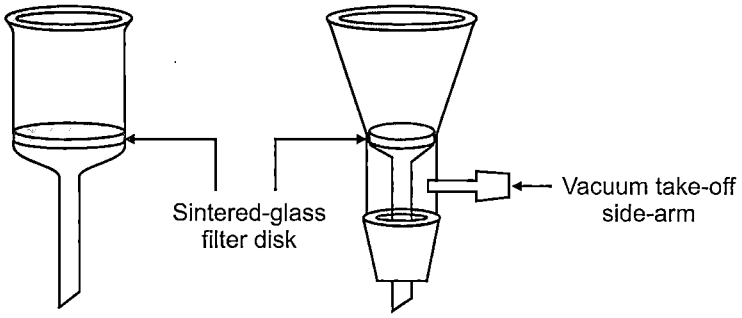


Fig. 4.16: Sintered glass filter and its assembly

(c) Working:

The porous fritted glass disc in the middle allows filtrate to drain through leaving solids behind. The filtration may be carried out under reduced pressure. The suction flask traps vacuum to ensure that no fluids are carried over from the vacuum pump to the evacuated apparatus or vice versa.

(d) Applications:

(1) It being permanent is used as an alternative to filter paper.

(2) For separation of viruses from bacteria.

(2) Sterilization of certain thermo-labile material.

(3) Filtration of broth cultures of bacteria.

4.6 DRYING

Drying is often a final step in production of pharmaceutical products. To material to be considered as "dried", the final product must be solid. The drying process involves a source of heat and a facility to remove the produced vapours. In majority of pharmaceutical intermediates or finished products the solvent removed is water. Desiccation may be synonymous with drying or considered an extreme form of drying. In pharmaceutical industry final product quality is never be compromised and the deterioration of the product may be due to presence of solvents. These solvents need to be removed at any cost using suitable drying operation.

(a) Definition:

Drying is a mass transfer process in which water or another solvent is removed by evaporation from a solid, semi-solid or liquid.

(b) Objectives:

Lack of understanding about the impact of the presence of moisture, environmental conditions and drying process parameters on drugs, critical product quality attributes, etc., creates challenges during product development, manufacturing, storage and use. In order to

improve and retain product quality such moisture sensitive products need to processed to remove solvents using drying. The main objective of drying is to preserve pharmaceutical products and increase their shelf life by reducing the water content and water activity. Its other objectives are to carryout size reduction; avoid deterioration and the need for use of refrigeration systems for transport and storage, which is expensive; to reduce space requirements for storage and transport; to minimize chemical changes, such as enzymatic and non-enzymatic browning, and to maximize therapeutic activity retention of bioactive compounds during drying.

4.6.1 Fluidized Bed Dryer

Fluidized bed dryer (FBD) is well known and widely used equipment in the pharmaceutical manufacturing. It is used in granulation process to attain desired moisture levels in the granules or powders required for perfect compression of tablet formulations. Conventional FBDs include batch fluidized bed dryer, semi-continuous fluidized bed dryer, well-mixed continuous fluidized dryer and plug flow fluidized bed dryer. Fluidized bed dryer has a high drying rate and the material is dried in a very short time. Material remains free-flowing and uniform.

(a) Principle:

The FBD works on a principle of fluidization of the feed materials. In this process, hot air is introduced at high pressure through a perforated bed of moist solid particulate. If air is allowed to flow through a bed of solid material in the upward direction with the velocity greater than the settling rate of the particles, the solid particles are blown-up and remain suspended in the air stream. Heat transfer is accomplished by direct contact between the wet solid and hot gases. Use of hot air to fluidizing the bed increases the drying rate.

(b) Construction:

A FBD contains a stainless steel chamber having a removable perforated bottom known as the bowl. A typical FBD, Fig. 4.17, consists of the air handling unit, product container, exhaust filter, exhaust blower, control panel, air distribution plate, spray nozzle, and solution deliver. The appropriate choice of distributor used during drying process ensures uniform and stable fluidization. The pressure drops across the distributor must be high enough to ensure good and uniform fluidization.

(c) Working:

Material to be dried is placed in the bowl type vessel. Air is introduced from the top and heated at required temperature by the heaters. The air is filtered through the filter and then passes through the bed of the material at the bottom. The airflow is generated by the fans fitted at the top of the equipment. The air flow rate and the operating temperature are adjusted by the control panel. As the flow of air increases, the bed expands and particles of powder start to rise up in a turbulent motion. The regular contact with air causes the

material to dry. The air leaving the FBD passes through the filter to collect the fine particles of the material. FBD bags have finger-like shape to increase the volume of the drying bed that helps to increase the drying rate and decrease the drying time. The vaporized liquid is carried away by the drying gases. Sometimes to save energy, the exit gas is partially recycled.

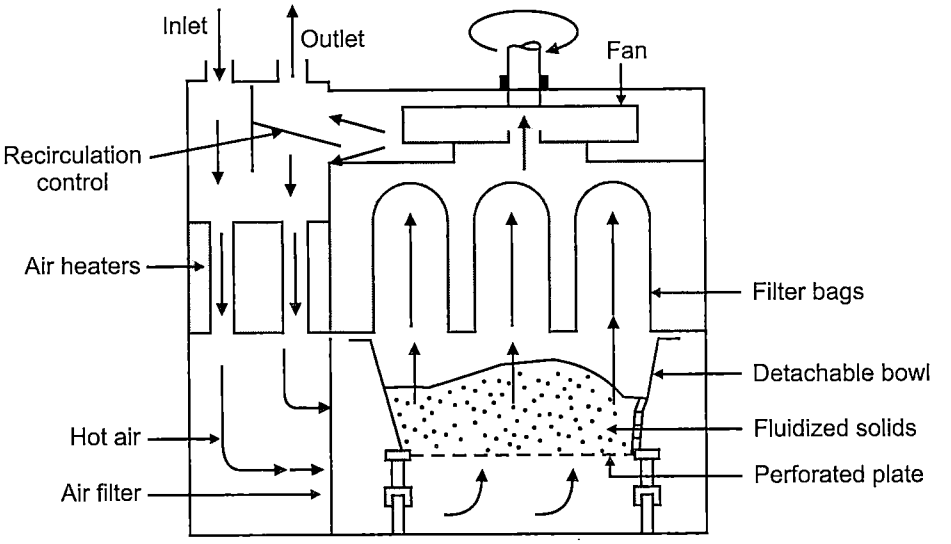


Fig. 4.17: Vertical Fluidized Bed Dryer

(d) Applications:

(1) FBD is used for drying and mixing of powders and agglomeration of materials.

(2) It is used in granulation and coating of powders, granules, tablets, pellets, beads.

(3) It is used as fluidized bed reactors, for solids separation and for heat/mass transfer.

(4) The modified FBDs are used in precision granulation, top spray granulation, spray drying granulation and granulation coating.

4.6.2 Freeze Drying

Freeze drying, also called lyophilization, is a process in which water is frozen, followed by its removal from the sample, initially by sublimation followed by desorption. The equipment used to dry solutions or suspensions at or below freezing points of liquids is called as freeze dryer or lyophilizer. Freeze drying is used in the manufacture of pharmaceuticals and biologicals that are thermolabile or otherwise unstable in water or moisture for prolonged storage periods, but that are stable in the dry state.

(a) Principle:

The principle involved in freeze drying is sublimation, where water passes directly from solid state (ice) to the vapour state without passing through the liquid state. Sublimation of water can take place at pressures and temperature below triple point of water (4.579 mm of

Hg at 0.0099 °C). The material to be dried is first frozen and then subjected under a high vacuum to heat (by conduction or radiation or by both) so that frozen liquid sublimes leaving only non-volatile solid, dried components of the original liquid. The concentration gradient of water vapour between the drying front and condenser is the driving force for removal of water during freeze drying.

(b) Construction:

Generally, there are three types of freeze dryers, for example, manifold freeze-dryer, the rotary freeze dryer and the tray style freeze-dryer. These freeze-dryers differ in the method by which the dried substance is interfaced with a condenser. The components common to all of them are a vacuum pump to reduce the ambient gas pressure in a vessel containing the substance to be dried and a condenser to remove the moisture by condensation on a surface cooled to –20 to –80 °C. A freeze dryer consists of a vacuum chamber wherein products to be dried are kept on shelves and capable of cooling and heating containers and their contents. A vacuum pump, a refrigeration unit, and associated controls are connected to the vacuum chamber.

(c) Working:

Traditional freeze drying is a complex process that requires a careful balancing of sample, equipment, and processing techniques. In this process, water is removed from a sample after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapour without passing through a liquid phase. It is performed at temperature and pressure conditions below the triple point of liquid, to enable sublimation of frozen material. The entire process is performed at low temperature and pressure. Steps involved in lyophilization start from sample preparation followed by freezing, primary drying and secondary drying, to obtain the final dried product. The vapour pressure of water increases with an increase in temperature during the primary drying. Therefore, primary drying temperature should be kept as high as possible, but below the critical process temperature, to avoid a loss of cake structure. There are four important stages in the complete freeze drying process namely pretreatment, freezing, primary drying and secondary drying.

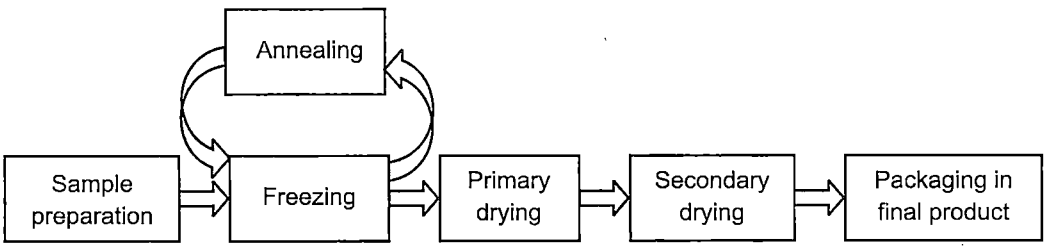


Fig. 4.18: Freeze Drying Cycle- Sequence of Operational Steps

(1) **Pretreatment:** In this stage product is treated for freeze concentration, solution phase concentration, preserve product appearance, stabilize reactive products, increase surface area, and decrease high vapour pressure solvents concentration prior to freezing.

(2) **Freezing:** During freezing stage usually the liquid sample is cooled down to −40 to −60 °C until pure crystalline ice forms from part of the liquid and the remainder of the sample is freeze-concentrated into a glassy state where the viscosity is too high to allow further crystallization.

(3) **Primary drying:** In primary drying the ice formed during the freezing is removed by sublimation under vacuum at low temperatures, leaving a highly porous structure in the remaining amorphous solute, that is typically 10% water. This step is carried out at pressures of 10^{-4} to 10^{-5} atmospheres, and a product temperature of −45 to −20 °C. The sublimation during primary drying is the result of coupled heat- and mass-transfer processes.

(4) **Secondary drying:** This is last step wherein most of the remaining water is desorbed from the glass as the temperature of the sample is gradually increased up to 10 - 15 °C while maintaining low pressures. Ideally, the final product is a dry cake with a high surface area and low moisture content (<3% w/w) which can be easily reconstituted.

(d) Applications:

(1) Freeze-drying is used to increase the shelf life of thermolabile products, such as vaccines and other injectable.

(2) It is used to enhance stability of products during storage, shipping, and transportation.

(3) Freeze-drying is used to reduce weight of products.

(4) It is used to preserve blood products in freeze-dried form.

(5) It is used in chemical synthesis to make products more stable and easier to dissolve in water.

(6) Freeze-drying can effectively be used in bio-separations in purification procedures.

(7) It can be used to concentrate low molecular weight substances that are too small to be removed by a membrane filtration.

4.7 EXTRACTION

Extraction is a process in which one or more components are separated selectively from a liquid or solid mixture (feed; phase 1), by means of a liquid immiscible solvent (phase 2). The transfer of the components from the feed to the solvent depends upon the solubility of each component in the corresponding phase. Two phases obtained upon extraction are

extract phase and the raffinate phase. The solvent is recovered by separation usually using distillation. Plant matrices contain a wide range of constituents that have various physical and chemical properties. These constituents need to be carefully, isolated from the rest of the plant matrices and make pure compounds of interest for their characterization and use.

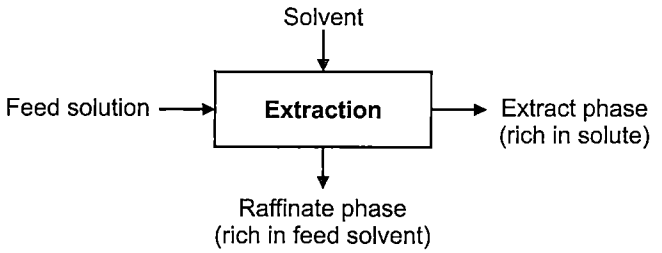


Fig. 4.19: Process of Extraction

The initial stage in extraction is the preparation of plant samples to preserve the biomolecules in the plants prior to extraction. Plants samples such as leaves, barks, roots, fruits and flowers can be extracted from fresh or dried plants material. Other pre-preparation of plant materials such as grinding and drying also influences the preservation of phytochemicals in the final extracts.

4.7.1 Definition

Extraction is the process of isolation of active ingredients from raw materials of either plants or animals or directly from the natural sources with the help of solvent.

4.7.2 Classification

The basic purpose of extraction is to obtain the therapeutically desirable portion and eliminate the inert material by treatment with a selective solvent known as the menstruum. Certain pharmaceutical preparations are prepared by extraction, that is, by withdrawal of desired constituents from crude drugs through the use of selective solvents in which the desired constituents are soluble. Types of extraction procedures play a crucial role for the qualitative and quantitative composition of the extracts. The standardized extracts, thus obtained are further processed for inclusion in other dosage forms.

Extraction can be classified as follows:

(1) Liquid-Liquid Extraction (Solvent extraction):

In this extraction the components of the liquid mixture are separated by contacting them with a suitable insoluble solvent which preferentially dissolves one or more components. Separation of the components from liquid mixture depends upon the unequal distribution of the components between two immiscible liquids. In this extraction the feed solution is phase 1 and the solvent used for extraction is phase 2. Both the feed and solvent forms a homogenous mixture which is separated by contacting them with one another to separate out one of the two liquids preferentially. This type of extraction is most widely used to separate actives and aromatic compounds from plants.

(2) Solid Phase Extraction:

Solid phase extraction is used for isolation, enrichment and purification of components from aqueous solutions depending upon their physical and chemical properties. It involves contacting of aqueous samples with a solid phase or sorbent, where the component under consideration is adsorbed on the surface of the solid phase prior to elution. The extract amount is negligible compared to quantity of analyte in the sample. This type of extraction is widely used in analytical laboratories.

(3) Solid-Liquid Extraction (Leaching):

Solid-liquid extraction means the removal of constituents from a mixture of solids by bringing the solid material into contact with a liquid solvent that dissolves these particular constituents. Leaching may either be used for production of concentrated solution of a active principle, or in order to free an insoluble constituents from a soluble material with which it is contaminated.

4.7.3 Methods

The purpose of extraction is to separate the soluble plant metabolites, leaving behind the insoluble cellular marc (residue). The initial crude extracts contain complex mixture of many plant metabolites, such as alkaloids, glycosides, phenolics, terpenoids and flavonoids. Some of the initially obtained extracts may be ready for use as medicinal agents in the form of tinctures and fluid extracts but some need further processing. Some of the commonly used extraction methods are discussed below.

(1) Maceration:

Maceration is a process that involves soaking of plant materials, usually in powder or coarse form, in a stoppered container with a defined solvent. The setup is left to stand at room temperature (±25 °C) for a minimum of 72 hours with shaking. The process is conditioned to soften and breakup the plant's cell wall in order to liberate the soluble bioactive metabolites. After 3 days, the whole mixture is pressed and sieved by filtration using Whatman no. 1 filter paper. In this method, heat is transferred by convection and conduction and the choice of the solvent is crucial to determine the type of phytochemical extracted from the samples.

(2) Percolation:

This is the most frequently used method to extract phytochemicals for the preparation of tinctures and fluid extracts. A percolator made of a narrow cone-shaped vessel open at both ends is generally used. The solid ingredients are moistened with a specified amount of the defined menstruum and allowed to stand for approximately 4 hours in a closed container. The wet mass is then packed and the top of the percolator is closed and some extra menstruum is added to form a shallow layer above the mass. This mixture is allowed to

macerate in the closed percolator for 24 hours. The outlet of the percolator is then opened and the liquid contained therein is allowed to drip out slowly. Further menstruum is added as required, until the percolate measures about three-quarters of the volume needed of the finished product. The macerated product is then pressed and the expressed liquid is added to the percolate. Sufficient menstruum is added to produce the required volume, and the mixed liquid is clarified by filtration or by standing followed by decanting.

(3) Decoction:

In decoction, the harvest crude product is boiled in a specified volume of water for a defined period, cooled and then strained or filtered. This procedure is applicable for the extraction of water-soluble, heat stable metabolites. The starting ratio of crude product to water is fixed, such as 1:4 or 1:16. The extract is then concentrated to one-fourth of its original volume by boiling. The concentrated extract is filtered and processed further. Decoction is generally suitable for extracting heat-stable compounds in hard plant parts such as the roots and barks. Decoction gives more oil-soluble phytochemicals compared to maceration and infusion.

(4) Digestion:

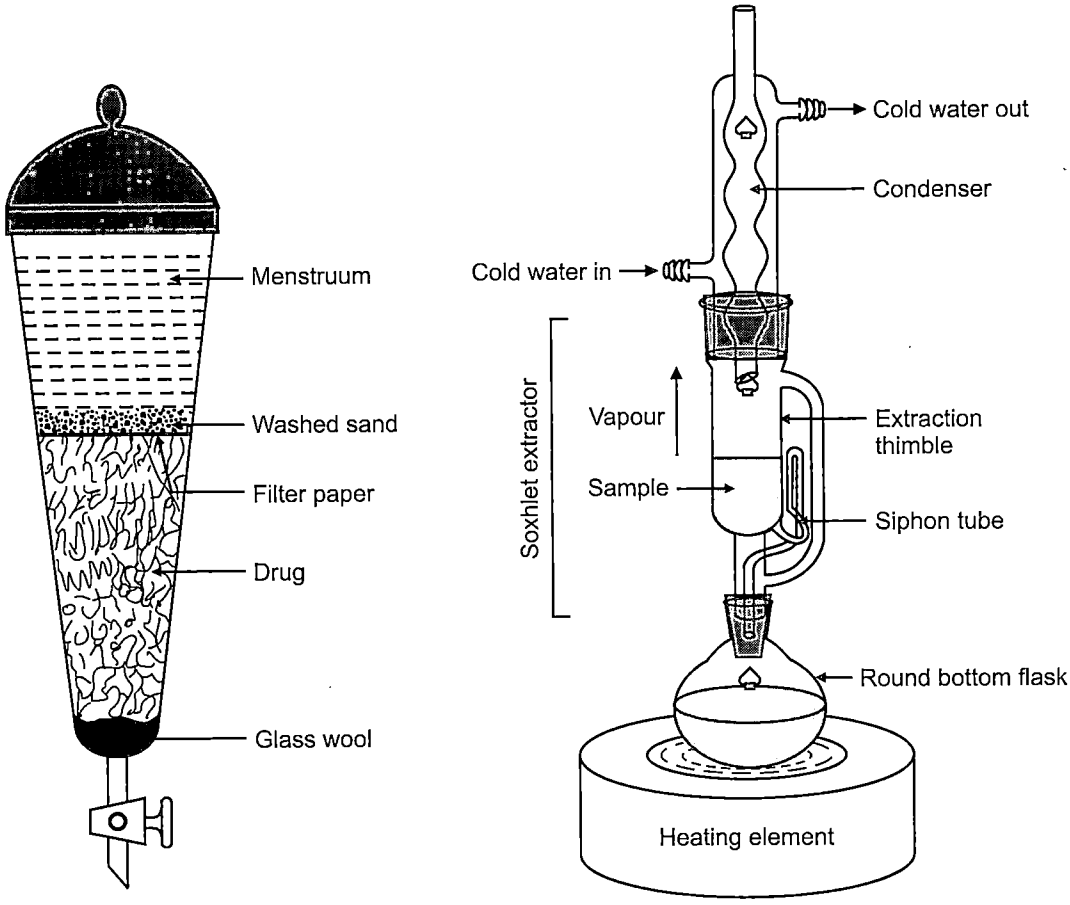
Digestion is a maceration method that includes application of gentle heat during extraction. It is used when a moderately elevated temperature is needed to increase the efficiency of the menstruum. In this process drug is extracted by heating at a particular pressure to increase the penetration power of the menstruum, so that there is complete extraction of the drug. The apparatus used is known as 'Digestor' which is a vessel made up of metal. The whole of the drug is placed in the covered digestor it and bolted with the help of nuts. The drug is treated with menstruum for a definite period under specified condition of temperature and pressure.

(5) Infusion:

Fresh infusions are prepared by macerating the crude drug for a short period with cold or boiling water. These are dilute solutions of the readily soluble constituents of crude drugs. Infusion uses the same principle as maceration; crude drug is soaked in cold or boiled water for shorter duration.

(6) Soxhlet Extraction (Hot continuous extraction):

In this method, finely ground crude drug sample is placed in a porous bag or thimble made from a strong filter paper or cellulose, which is placed in thimble chamber of the Soxhlet apparatus. Extraction solvent is heated in the round bottom flask, vaporizes into the sample thimble, and condenses in the condenser and drip back. When the liquid content reaches the siphon arm, it is emptied into the bottom flask again and the process is continued.



(a) Percolator **(b) Soxhlet**

Fig. 4.20: Extraction Apparatus

(7) Microwave Assisted Extraction (MAE):

MAE utilizes microwave energy to facilitate partition of analytes from the sample matrix into the solvent. Microwave radiation interacts with dipoles of polar and polarizable materials (solvent and sample) that causes heating near the surface of the materials and heat is transferred by conduction. Dipole rotation of the molecules induced by microwave electromagnetic disrupts hydrogen bonding; enhancing the migration of dissolved ions and promotes solvent penetration into the matrix. In non-polar solvents, poor heating occurs as the energy is transferred by dielectric absorption only. MAE can be considered as selective methods that favour polar molecules and solvents with high dielectric constant.

(8) Sonication Extraction:

This method involves the use of ultrasound waves ranging from 20 kHz to 2000 kHz. The mechanic effect of acoustic cavitation from the ultrasound waves increases the surface contact between solvents and samples and permeability of cell walls. Physical and chemical properties of the materials subjected to ultrasound are altered and disrupt the plant cell

wall; facilitating release of compounds and enhancing mass transport of the solvents into the plant cells. The procedure is simple and relatively cheap that can be used in both small and larger scale of phytochemical extraction.

(9) Accelerated Solvent Extraction (ASE):

ASE is an efficient form of liquid solvent extraction due its minimal solvent requirement. Sample is packed with inert material such as sand in the stainless steel extraction cell to prevent sample from aggregating and block the system tubing. Packed ASE cell includes layers of sand-sample mixture in between cellulose filter paper and sand layers. ASE is an automated extraction technology capable of controlling temperature and pressure for each individual samples and completes in less than an hour.

(10) Supercritical Fluid Extraction (SFE):

Supercritical fluid (SCF; dense-gas) is a substance that shares the physical properties of both gas and liquid at its critical point. Factors such as temperature and pressure are the determinants that push a substance into its critical region. SCF behaves more like a gas but have the solvating characteristic of a liquid. For examples, CO_2 become SCF at above 31.1 °C and 7380 kPa. Use of SCF-CO_2 is popular because it is excellent solvent for non-polar analytes and CO_2 is readily available at low cost and has low toxicity. Even though SCF-CO_2 has poor solubility for polar compounds, modification such as addition of small amount of ethanol and methanol enable it to extracts polar compounds. A major drawback of this method is the initial cost of the equipment which is very high.

Although ASE and SFE are used in the extraction of plant materials they are less popular because of their high costs despite the efficiency of these methods.

4.7.4 Applications

The operation of extraction is applied in almost every area of pharmaceutical and chemical industry.

(1) It is used in the separation of antibiotics and protein recovery.

(2) It used to recover high-boiling components such as phosphoric acid, boric acid, and sodium hydroxide from aqueous solutions.

(3) It is used to obtain therapeutically active constituents from plant parts and to eliminate the inert material. For example, strychnine from nux-vomica, quinine from cinchona bark, and morphine from opium and reserpine from Rauwolfia serpentina.

(4) It is used to isolate enzymes (renin) and hormones (insulin) from animal sources.

(5) Gelatin is produced by conversion of skin and bone collagen by treatment with lime or diluted acid and is further extracted with warm water.

(6) It is used in extraction of fixed oils from seeds.

REVIEW QUESTIONS

1. What is unit operation? What is the basis of unit operations?
2. What is significance of studying unit operations?
3. Name various unit operations used in pharmaceutical field.
4. Define size reduction. What are its objectives?
5. Describe principle, construction, working and applications of hammer mill.
6. Describe principle, construction, working and applications of ball mill.
7. Define size separation. What are its objectives?
8. Classify powders according to IP.
9. Describe principle, construction, working and applications of cyclone separator.
10. What is sieve? Write about its construction and types.
11. List out applications of sieves.
12. Describe standards for sieves.
13. Define the terms: sieve number, nominal size, nominal diameter and approximate percent sieve area.
14. Name international standards used for types of sieve.
15. Define mixing. What are its objectives?
16. Describe principle, construction, working and applications of double cone blender.
17. Describe principle, construction, working and applications of turbine mixer.
18. Describe principle, construction, working and applications of triple roller mill.
19. Describe principle, construction, working and applications of Silverson mixer.
20. Describe principle, construction, working and applications of homogenizer.
21. Discuss various types of homogenizers used for pharmaceutical applications.
22. Define filtration. What are its objectives?
23. Define the terms: filter medium, slurry, filter cake and filtrate.
24. Discuss theories of filtration.
25. What is Kozeny-Carman equation?
26. What is Poiseuille's law?
27. What is Darcy's equation?
28. Describe principle, construction, working and applications of membrane filter.
29. Describe principle, construction, working and applications of sintered glass filter.
30. Define drying. What are its objectives?

31. Describe principle, construction, working and applications of fluid bed dryer.
32. Define the terms: freeze drying, primary drying and secondary drying.
33. Describe principle, construction, working and applications of freeze dryer.
34. Define extraction. What are its objectives?
35. Discuss general process of extraction.
36. Enlist types of extraction giving examples.
37. What is solvent extraction and leaching?
38. Defines the terms: maceration, percolation, decoction, infusion, digestion, .
39. Enlist are pharmaceutical applications of extraction.

Chapter ...5

PHARMACEUTICAL FORMULATIONS

♦ **LEARNING OBJECTIVES** ♦

After completing the chapter, students will be able to:

- Know basic concepts of pharmaceutical formulations.
- Define, classify pharmaceutical products.
- Understand manufacturing techniques of pharmaceutical products.
- Describe quality control tests used for pharmaceutical products.
- Understand storage conditions for pharmaceutical products.

5.1 TABLETS

Oral route of administration is the most preferred route because of ease of ingestion, avoidance of pain and patient compliance. Drugs may be administered orally as tablets that contain a dose of drug which is given as a single unit. Amongst all the solid dosage forms, tablet is the most popular and commonly administered dosage form because of its convenience in self administration, its compactness and ease of manufacturing. According to the Indian Pharmacopoeia pharmaceutical tablets are solid, flat or biconvex unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without diluents. Tablets may vary in size, shape, weight, hardness, thickness, disintegration and dissolution characteristics and in other aspects, depending on amount of medicament/s, their intended use and method of manufacture. All drugs can be formulated as tablet form except when it is difficult to formulate or administer them.

Tablets constitute approximately 90% of all dosage forms clinically used to provide systemic administration of drugs. The major classes of tablets include uncoated and coated tablets. Tablet coating is the outer covering of a tablet with a layer/substance. The coats used range from the traditional sugar coating to the present polymer and polysaccharide based coats. The types of coats depend on the specific functionality of the tablet as well as the target consumer of the tablet. The types of tablet coating used to enhance specific functionality ranges from obscuring bitter taste of the drugs, creating a smooth covering to promote easy swallowing, protecting from damage or external forces, creating a branded pill for marketing purposes as well as increasing the shelf life of the tablets.

(a) Advantages of Tablets:

1. Tablets are unit dosage form with greatest dose precision and least content variability.
2. Tablets are produced at large scale and have elegant appearance and low cost.
3. Tablets being lighter and compact are easiest and cheapest to package and strip.
4. Tablets are easy to swallow and have least tendency to hang-up.
5. Drugs with objectionable odour and bitter taste can be masked to improve patient acceptability by coating the tablets.
6. Tablets have greatest physical, chemical and microbial stability.
7. Tablets may contain two or more drugs even if they are physically or chemically incompatible and thus reduces multiple administrations.
8. Tablets can be designed to release drugs at a particular site within the GIT to promote absorption at that site, reduce side effects and provide a local effect.

(b) Disadvantages of Tablets:

1. Tablets are difficult to swallow by children and unconscious patients.
2. Some hydrophobic and low density drugs may not be compressed into tablet.
3. Drugs with poor wetting and slow dissolution are difficult to manufacture as a tablet.
4. Tablet manufacturing involves an increased level of product loss during processing.
5. The absorption of drug from tablets depends on gastric residence or emptying time, and thus it varies from patient to patient.

5.1.1 Coated Tablets

Tablet coating is a process of applying film of materials on the surface of pharmaceutical tablets to achieve special benefits. The amount of coating on the surface of a tablet is critical to the effectiveness of the oral dosage form. This additional process increases the cost of tablet production. Tablets are usually coated in horizontal rotating pans with the coating solution sprayed onto the free surface of the tablet bed. When a coating solution is applied to a batch of tablets, the surfaces of the tablets get covered with a tacky polymeric film. The tablets are then allowed to dry using suitable means and the film eventually forms a non-sticky dry surface. The coating technique involves parameters such as the spray pattern, drop size, and nozzle spacing, etc., which must all be precisely controlled in order to ensure uniform distribution of the coating material. Tablet coating is relatively costly process that has high bulk due to the use of other coating materials. It is tedious and time-consuming process that requires the expertise of highly skilled technician.

The objectives of tablet coating include improving aesthetic quality by incorporating special colours, mask the disagreeable odour, colour or taste, offer product stability through physical/chemical protection, control and sustain the release of the drug, incorporate two or

more incompatible drugs, protect an acid-labile drug from the gastric environment, increase mechanical strength of tablets, etc. Tablet coating machines are used to coat the surface of tablets with a thin coating of film. There are many types of machines used to coat tablets. Depending on the working principle, tablet coating machines can be classified as standard coating pan, perforated coating pan and fluidized bed coater. Every type of tablet coating machine tends to have a unique working principle. Basically, this implies that the structural design will also be different.

(a) Types of Coated Tablets:

Different types of tablets need different coating according to the nature and properties of the tablets. The types of coats applied on tablet surface depend on the specific functionality of the tablet as well as the target consumer of the tablet.

(i) Sugar coated tablets: A sugar-coated tablet is coated with sugar to disguise the taste. These tablets are prepared by suspending uncoated tablets in an air and applying coating solution into the air stream. Sugar coating offers a sweet coat mainly made from polysaccharides and sucrose to obscure the bitter taste of the tablet. It also offers a sweet aroma especially on foul smelling pills like fish supplements. The sugar syrup is coated on the tablet and water is left to evaporate from the syrup leaving a sugar coat that can either be coloured or uncoloured. Sugar coating adds a 30% more weight to the tablet. This coating is soluble, masks bad taste, acts as a protective layer and enhances appearance. The coating results in a highly flavoured and shiny tablet. Sugar coated tablets are prepared especially for kids.

Examples: Hyoscine butylbromide Sugar Coated Tablet (Sanofi), Ibuprofen Sugar Coated Tablet (Bristol), Premarin 0.625 mg Sugar Coated Tablet (Pfizer), etc.

(ii) Film coated tablets: A film-coated tablet is covered with a thin layer of resins, polymers and/or plasticizers capable of forming a film. Film coating is a process of adding a very thin layer to tablets. The coating gives aesthetic look and improves the taste of the pill. Tablets especially those from herbal extracts are not visually pleasing, therefore a coating is necessary for beautifying the tablet using different colours. Spraying is used to create an even film around a tablet. Film coating produce a stable and strong tablet. Film coating process is easy to automate, involves few procedures and increases the overall weight of tablets by about 3%. Coating can be useful in tablet branding and for identification.

Examples: Metformin Film Coated Tablet (Wockhardt), Atenolol Film Coated Tablet (Teva), Atorvastatin Film Coated Tablet (Milpharm), etc.

(iii) Gelatin coated Tablets: Gelatin-coated tablets are compressed tablets coated with either one or two-toned colour gelatin. Gelatin is a natural binding, coating and disintegration agent used to create the gel cap, a capsule-shaped tablet as the outer covering. It produces a tablet rich in protein with lustrous appearance and a pleasant mouth feel. These tablets are easy-to-swallow, have custom branding, prevent counterfeit, are tamper-evident, mask unpleasant odours or flavours; improve stability of photosensitive drugs, and looks like softgels. They are also ideal for double-blind clinical studies, or for

drugs that can irritate the esophageal mucosa when they are incorporated in immediate-release tablets.

Examples: Famtac Gelatin Coated Tablet (Abbott Healthcare), Glucosamine and Chondroitin Gelatin Coated Tablet (Zynova), Famotidine Gelatin Coated Tablet (Universal Drug), etc.

(iv) Enteric coated tablets: An enteric-coated tablet is one that is designed to temporarily withstand attack by stomach acid, so that it does not dissolve in the stomach but allows release of the medication in the intestine. Enteric coating provides a gastric acid resistant coat for the tablets that have ingredients sensitive to stomach acid. If a drug from tablet is to be absorbed in the small intestine, there is a need for the tablet to withstand gastric acid and reach the targeted area in the lower part of GIT where there is no acidity and is absorbed slowly. This type of tablet need not be crushed or chewed to prevent the risk of damage due to a reaction with gastric acid. Enteric coating helps to deliver the tablet to intestine without damaging effects to the drug or consumer.

Examples: Diclofenac and Serratiopeptidase Enteric Coated Tablets (DSV Healthcare), Erythromycin Enteric-Coated Tablet (AdvaCare), Omeprazole Magnesium Enteric-Coated Tablet (Glow Sun India), Aspirin Enteric-Coated Tablet (Teva), etc.

(v) Compression coated tablets: Compression coated tablet covers bitter or unpleasant substance and mottled appearance, or provide a barrier for a substance irritating to the stomach or one inactivated by gastric juice. Most drugs that are compression-coated contain two materials separated into two parts. The outer coat is typically a water-soluble sugar compound that dissolves after swallowing. The internal core usually contains an enteric coating that allows for a second drug to release during a later digestive stage. The internal core may be liquid to allow for simultaneous release with the outer coat. It involves compaction of granular particles around a preformed tablet using special equipment through a drying process.

Examples: Sumatriptan Succinate Tablet (Glaxo), Glipizide Tablet (Care Formulation Lab), Nifedipine Retard 20 mg Tablets (Taj Pharma), etc.

(b) Coating Process:

The tablet coating process involves three significant requirements:

(1) Tablet quality: The tablets processed for coating are tough enough to tumble during coating and drying. The tablets must be consistent in porosity and hardness as well as must be free of dust, must not break apart during the preheat cycle at the start of the coating process or during the first few minutes of exposure to the atomized solution.

(2) Construction of coater: A general tablet coating system comprises of a coating pan, a spraying system, an air handling unit, a dust collector, and the controls.

(3) Coating operation: It involves loading batch of dedusted and preheated tablets into the coating pan, spraying coating solution and its distribution and drying.

(c) Defects in Tablet Coating:

During coating tablets several defects can arise, which may include:

(1) Blistering: The blistering in tablet coating is a local detachment of film from the substrate forming blister.

(2) Cratering: It is defect of film coating whereby volcanic-like craters appears on the tablet which in turn results in the exposure of the tablet's surface.

(3) Picking: It is defect where isolated areas of film are pulled away from the surface when the tablet sticks together or when part of the film sticks to the pan that result in some of the tablet pieces being detached from the core.

(4) Pitting: It is defect whereby pits (deformation) occur in the surface of a tablet core without any visible signs of disruption of the film coating.

(5) Blooming: It is defect where coating becomes dull immediately or after prolonged storage at high temperatures.

(6) Blushing: It is nothing but haziness or appearance of white specks in the tablet film.

(7) Colour variation: It involves variation in colour of the tablet film within a batch.

(8) Infilling: It is defect that renders the intagliations indistinctness.

(9) Orange peel: It is surface defect resulting in the film being rough and matt.

(10) Cracking/Splitting: It is defect in which the film either cracks across the crown of the tablet or splits around the edges of the tablet.

(11) Bridging: It occurs when the coating fills in the lettering or logo on the tablet surface.

(12) Scuffing: Scuffing involves the generation of gray-to-black marks on the surface of white (or lightly coloured) film-coated tablets.

(13) Twinning: This twinning is used when two or more tablets stick together.

5.1.2 Uncoated Tablets

The main objective of the tablet formulation design is to deliver orally correct amount of drug in the proper form over proper time and at desired location, so as to have suitable chemical integrity protected at the point of its action. The physical design and complete chemical makeup of the tablet can have a profound effect on the efficiency of the drug being administered. In general, the tablet formulation comprises of a mixture of drug(s) and excipients, usually in powder form. A tablet is usually a composed of 5-10% of the drug, 80% of fillers, disintegrants, lubricants, glidants, and binders; and other compounds which ensure easy disintegration, disaggregation, and dissolution of the tablet in the stomach or the intestine.

(a) Granulation Methods:

Granulation is a technique of particle enlargement by agglomeration. It is one of the most significant unit operations in the production of tablets. During this process, small fine or coarse particles are converted into large agglomerates called granules. Generally, granulation begins after initial dry mixing of the powder ingredients along with the drug(s), so that a uniform distribution of each ingredient throughout the powder mixture is achieved. Granules prepared in the making tablets have particle size in the range of 0.2-4.0 mm. Granules are produced as an intermediate with a size range 0.2-0.5 mm to be mixed with other excipients before compaction. Granules are produced to attain the uniformity of the drug content in the final product, to increase the density of the blend so that it occupies less volume per unit weight for better storage and shipment, to facilitate metering or volumetric dispensing, to reduce dust during granulation process to reduce toxic exposure and process-related hazards, and to improve the appearance of the product.

The granulation is widely used method which further categorized in to two types based on the type of method used to facilitate the agglomeration of powder particles, namely; dry granulation and wet granulation. Granulation technologies like roller compaction, spray drying, supercritical fluid, low/high shear mixing, extrusion/spheronization and fluid bed granulation have been successfully used for preparation of various tablets.

(i) Tablet molding: In this technology, generally water-soluble ingredients are used so that tablet disintegrate and dissolve rapidly in the GI fluid upon administration. The powder mixture is moistened with a hydro-alcoholic solvent and is molded into a tablet using compression pressure lower than that used in conventional tablets compression. It is followed by solvent removal using air-drying method. Tablets produced by molding have a porous structure that enhances its dissolution, low mechanical strength and poor taste masking characteristics. Therefore, binders are employed to increase the mechanical strength of tablets prepared by molding technique.

(ii) Wet granulation: Wet granulation is a process of using a binder in liquid form as dispersion to lightly agglomerate the different powders as a blend. This process simply involves multiple unit processes such as wet massing of the powder blend with a granulating liquid, wet screening, drying and compression, which are complex, time consuming, and expensive requiring large space and multiple equipment. The amount of binder fluid used in agglomeration needs to be critically controlled so as to form wet mass of desired consistency. Over-wetting causes the granules to be too hard and under-wetting causes them to be too soft and friable during handling. Aqueous dispersions being safer are suitable for drugs which are not degraded by hydrolysis.

(iii) Dry granulation: The dry granulation process is used to form granules without using a heat and liquid solution because the product to be granulated may be sensitive to moisture and heat. This method uses mechanical compression called slugs or compaction using rollers to facilitate the agglomeration of dry powder particles. It is the least desirable of all granulation methods. Forming granules without moisture requires compacting and densifying the powders. There are two methods used for dry granulation.

Slugging: In this method, the powder is precompressed and the resulting compacts or slugs are milled to yield the granules. If a tablet press is used for the compaction process, the term slugging is used.

Roller compaction: In this method, powder is precompressed with pressure on a tablet press using slugging tools or on a roller compactor called Chilsonator.

(iv) Direct compression: The term direct compression is defined as the process by which tablets are compressed directly from powder mixture of drugs and suitable excipients. The mixture for compression has adequate flow properties and coheres under pressure. In this method no pretreatment of the powder blend by wet or dry granulation is required.

(b) Example of Uncoated Tablet Formulation:

Acetylsalicylic Acid (ASA) is a non-steroidal anti-inflammatory drug that inhibits platelet aggregation. The components and their contribution in formula are presented in Table 5.1.

Table 5.1: Formulation table for acetylsalicylic acid effervescent tablets

Ingredients	mg/tablet	Contribution (%)
Acetylsalicylic Acid	500.0	12.5
PRU® (Sodium Stearyl Fumarate)	12.0	0.3
Citric acid	348.0	8.7
Sodium bicarbonate	400.0	10.0
Glycine hydrochloride	128.0	3.2
Aspartame	76.0	1.9
Flavour	36.0	0.9
DAM® (Dextrates)	2,500.0	62.5
Total	4,000.0	100.0

Procedure: All ingredients except PRU® are blended for 15 minutes. PRU® is added and the powder mixture is mixed for another 3 minutes. Now the powder mixture is ready for direct compression. Equipment used is tablet press and turbula mixer, tablet diameter is 25 mm with biplane shape. The instruments used for quality control testing include tablet hardness tester, friability tester, disintegration test apparatus, dissolution test apparatus and spectrophotometer.

5.1.3 Various Modified Tablets

The term modified tablet is used to describe products that alter the timing and/or the rate of release of the drug. Modified tablets are designed to release their medication in controlled manner, at pre-determined rate, duration and location in the body to achieve and maintain optimum therapeutic blood levels of drug. These dosage forms have been developed to deliver drug to the part of the body where it will be absorbed, to simplify dosing schedules, and to assure that concentration of drug is maintained over an appropriate time interval. Drugs with short half life usually require multiple daily dosing to

achieve the desired therapeutic effects. Multiple daily dosing is often inconvenient and can result in missed doses, made-up doses and patient non-compliant with therapeutic regimen. Modified tablets provides several advantages such as less frequent administration, more reproducible dispersion throughout the gastrointestinal tract, reduction in drug release variations and an improved bioavailability. Unfortunately, they have risks of spontaneous drug release from a single-unit tablet due to damage the coating or its attachment in the stomach or intestine causing an irritation of the gastric or intestinal mucosa, which can be reduced by the use of multiunit tablet forms.

Modified-tablets involves various mechanisms to dissolve a drug over time in order to be released slower and steadier into the body thus requires less frequent administration with reduced side effects than immediate-release formulations of the same drug.

5.1.3.1 Sustained Release Tablets

Sustained drug release systems include any drug delivery system that achieves slow release of drug over an extended period of time. Sustained release tablet is unit solid dosage form through which drug is administered to a patient at a given rate to maintain a certain concentration of the administered drug over a specific time period into the patient's body while reducing possible side effects. These tablets provide actual therapeutic control that would be temporal (time related), spatial (site related) or both.

The advantages of sustained release tablets include reduced drug concentration fluctuations in the body, reduction in drug dose, improved patient compliance and safety of drugs. The major limitations of these tablets are chance of dose dumping, difficulty in dose retrieval, high cost of production, need for additional patient education and reduced potential for accurate dose adjustment. The performance of a drug administered as a sustained release tablets depends upon its release from the formulation and movement within the body during its passage to the site of action. These tablets are more of a controlled and time-release type that can either release part of drug (loading dose) immediately or in small amounts (maintenance dose) after administration. Time and rate of administration of these tablets is predetermined so as to reduce blood level fluctuations or reduce effects on the intestinal tract and even extend the drugs half life.

The desired biopharmaceutical properties of a drug to be used in sustained release tablets includes molecular weight, aqueous solubility, apparent partition coefficient, pKa and ionization at physiological pH, stability and route of administration. The formulation strategies for oral sustained release tablets includes (i) Diffusion sustained release (ii) Dissolution sustained release (iii) pH dependent system (iv) Altered density system (v) osmotic pump system and (vi) ion exchange system.

Examples: Acebrophylline Sustained Release Tablet (Jantec), Paracetamol Sustained Release Tablets (Aspire Remedies Pvt Ltd.), Indapamide Sustained Release Tablets IP (Care Formulations Lab), etc.

5.1.3.2 Extended-Release Tablets

Extended-release (ER) tablet is a dosage form that allows at least a two-fold reduction in dosing frequency as compared to an immediate-release (conventional) tablet. They also differ from immediate release tablets which release content within few minutes of ingestion. ER tablets slowly release drug into the body over a period of time, usually 12 hours or 24 hours and are only taken once or twice a day. They are specially designed to release a pre-designated amount of medication throughout the day.

(a) Advantages: ER tablets offer several advantages which include less frequent dosing, fewer side effects, less fluctuations in blood levels, complete absorption, potential to improved patient compliance and convenience, increased stability, improved bioavailability, providing special effects, etc.

(b) Disadvantages: The major disadvantage of ER tablets include slower onset of action and comparatively high cost. In addition, in the event of adverse drug reactions, ER tablets may show side effects that may remain for a much longer period of time. The higher drug load in these tablets may cause loss of integrity of the release characteristics. The size of ER tablet may cause difficulties in ingestion or transit through gut. The drug release rates are affected by presence of food in GIT. Sometimes the target tissue is exposed to constant amount of drug over extended period resulting in drug tolerance.

ER tablets may also be known as controlled release (CR), sustained release (SR), time release (TR), long acting (LA), extra time (XT), extra long (XL), delayed release (DR), enteric coated (EC), modified release (MR), sustained action (SA) and continuous control (CC). ER tablets should be taken as prescribed and should not be crushed, splited or chewed. ER tablets can result in an overdose if crushed or chewed. Air or moisture can change the effectiveness of ER tablets, so it is important to store them in sealed bottles and in a dry place. Altering the original form of an ER tablets can make it less effective.

Examples: Divalproex Sodium Extended Release Tablet (Synko Healthcare Limited), Carvedilol Phosphate Extended Release Tablet (Ace Kinetics), Ranolazine Extended Release Tablet (Taj Generics), Venlafaxine Extended Release Tablet (Talent Health care).

5.1.3.3 Fast Dissolving Tablets

Fast dissolving tablets (FDT) are solid dosage forms designed to dissolve in saliva remarkably faster, within a few seconds (usually less than 60 sec.), and those are real fast-dissolving tablets. FDTs disintegrate rapidly in saliva without the need to take water and are commonly used for the pediatric and geriatric patients who have difficulties such as fear of choking while swallowing them with water or have difficulties in chewing them. Sometimes very elderly patients of depression may not be able to swallow conventional tablets. FDTs can also be known as orally disintegrating or dispersible tablets (ODTs), mouth melting tablets (MMTs) or mouth dissolving tablets (MDTs), immediate release (IR) tablets.

Mouth dissolving tablets are formulated by use of super disintegrants like Croscarmellose sodium, sodium starch glycolate and crospovidone or by maximizing pore

structure of the tablets by freeze drying and vacuum drying. The processed powder mixture is directly compressed because of its quick and easy procedure and cost effectiveness. The bioavailability of some drugs may be increased by formulating them as FDT due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to conventional tablets.

(a) Advantages: Various advantages of FDTs include no need of water to swallow the tablet, easy administration to pediatric, elderly and mentally disabled patients, accurate dosing, faster dissolution and absorption of the drug offering rapid onset of action, increased bioavailability, reduced first pass metabolism, improved safety and high drug loading.

(b) Disadvantages: The major disadvantage of FDT is its mechanical strength. FDTs being highly porous, soft molded metrics or compressed with low compressional pressure, are friable and brittle which make them difficult to handle. Bad taste/odour drugs are difficult to formulate as FDT. Several of the FDT are hygroscopic and thus cannot maintain its physical integrity under normal humidity condition and thus requires specialized package. Dryness of the mouth due to decreased saliva production may hamper dissolution, rate of absorption from the saliva solution and overall bioavailability.

Many techniques are used for production of FDTs that include freeze drying, tablet moulding, and spray drying, sublimation, direct compression and mass extrusion.

Examples: Piroxicam Fast Dissolving Tablet (Pfizer), Rizatriptan Fast Dissolving Tablet (Merck and Co.), Ondensetron (Glaxo Wellcome), Rofecoxib Fast Dissolving Tablet (Torrent), Montelukast (Ranbaxy), Zolmitriptan Fast Dissolving Tablet (AstraZeneca), etc.

5.1.3.4 Double Layered Tablets

Double-layer tablets (DLT), often called Bilayer tablets, are controlled (gradual) release formulations that have a combination of two or more drugs in a single tablet. DLT technology separates two incompatible drugs in which one layer is immediate release as a loading dose, and the second layer is controlled/sustained release as a maintenance dose. Two incompatible drugs can also be formulated into a bilayer tablet by adding an inert intermediate layer. These tablets make it easier for patients, because they can reduce the number of daily doses required, to simplify dosage regimens.

In DLT, compressing separate layers of each drug minimizes the area of contact between two layers. An additional intermediate layer of inert material may also be included to ensure the layers don't make contact. To produce adequate tablet formulation, specific requirements, such as sufficient mechanical strength, and the desired drug release profile, must be met. The compaction of the material consists of both compressibility and consolidation. DLTs are prepared by single-sided tablet press, double-sided tablet press, and bilayer tablet press with displacement monitoring.

(a) Advantages: DLTs offer greatest dose precision and the least content variability. They are lighter and compact, easiest and cheapest to package and strip, easy to swallow with least tendency for hang-up, can mask objectionable odour and bitter taste and are suitable for large scale production. In addition, it has greatest chemical and microbial stability, easy and rapid product identification requiring no additional steps.

(b) Disadvantages: DLT manufacturing is more expensive than single-layer tableting such as high tablet press costs, slow operation in bilayer mode and more time spent on formulation development, analysis, and validation. Other disadvantages include layer separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield, etc.

Examples: Glimipride & Metformin Hydrochloride (SR) Bilayer Tablets (Angiolife Healthcare), Diclofenac Potassium Paracetamol Double Layer Tablet (Angiolife Healthcare), Tramadol, Acetaminophen Bilayer Tablet (Taj Pharma), Amlodipine Besilate Metoprolol Succinate Bilayer Tablets, etc.

Quality Control Tests:

Finished product quality control tests (FPQC) for tablets are performed according to Pharmacopoeial and in-house specifications.

(1) Appearance: Appearance of a tablet is determined directly by observing tablets for elegance, shape, size, colour, surface textures, presence or absence of odour and taste.

(2) Unique identification markings: National Drug Code (NDC) number, product name and product potency markings on the tablet are verified visually.

(3) Size and shape: Size and shape of a tablet is determined by its thickness using Vernier caliper. A thickness with ±5% may be allowed, depending on tablet size.

(4) Hardness: Hardness of tablet is an indication of its strength and is determined by Monsanto or Pfizer hardness tester. It is measured in kg/cm^2.

(5) Weight variation: This test ensures uniformity in weight of tablets in a batch. The total weight of 20 tablets selected randomly from a whole batch is determined and the average weight is calculated. Coated tablets are exempted from this test.

(6) Friability test: Friability is the loss of weight of tablet during transportation or handling. Measurement of friability is performed using Roche friabilator. The procedure involves random selection of tablets that weighs with a unit mass ≤650 mg. A maximum mean mass loss from the 3 samples of not more than 1.0% is considered acceptable.

(7) Wetting time: The wetting time of the ODTs is measured using five circular tissue papers placed in a petridish containing 0.2% w/v amaranth solution. A tablet is placed on the tissue paper and the time required to develop blue colour on the upper surface is noted.

(8) Water absorption ratio: A small piece of tissue paper folded twice is placed in a small petridish containing water. A tablet is placed on the paper and allowed to wet. The wetted tablet is weighed and the difference in weight is used to determine absorption ratio.

(9) Disintegration test: This test is conducted with the help of USP tablet disintegration test apparatus. The sample of tablets complies with the test if disintegrates within 15 min for uncoated tablets, 30 min for plain tablets, and 60 min for coated tablets and pills.

(10) Drug uniformity: In this test 10 tablets are crushed to form powder of which powder equivalent to 100 mg drug is dissolved in suitable media to make up 100 mL solution. The resultant solution is filtered, diluted 100 times and analyzed spectrophotometrically to determine drug content in a tablet.

(11) Uniformity of dispersion: To perform this test two tablets are kept in 100 mL distilled water and gently stirred for 2 min. The dispersion is passed through 22 mesh sieve. The tablets are considered to pass the test if no residue remains on the screen.

(12) Dissolution test: This test is carried out in USP dissolution test apparatus using specified volume of dissolution media maintained at 37±0.5 °C. The tablets are kept in the cylindrical basket or directly placed in 900 mL medium in vessel and the medium is stirred at specified rpm. Within the time interval specified, a specific amount of medium is withdrawn from the vessel and same volume of fresh medium is replaced each time. The samples are analyzed spectrophotometrically to determine amount of drug released at specific time.

(14) Stability testing: Stability testing allows the establishment of storage conditions, retest periods, and product shelf-life and expiry dating. A combination of temperature and humidity is used to evaluate the stability of tablets. In storage chamber temperature is controlled within ±2 °C, and the relative humidity is controlled within ±5%.

5.2 CAPSULES

The concept of encapsulation of drugs is a popular method and used in many dosage forms to enclose drugs in a relatively stable shell (capsule) which is taken orally or be used as suppositories. Mathes in 19th century developed the first capsule from gelatin and since then this technology has been continuously improved and refined. Capsules are made of gelatin shells filled with substances in dry powders, semi-solids, and liquids that do not dissolve in gelatin and make up an individual dose.

(a) Definition:

Capsule can be defined as solid dosage form in which the drug substance is enclosed in either a hard or soft, soluble shell of gelatin or other suitable material.

EurPhar describes capsules as 'solid preparations with hard or soft shells of various shapes and capacities, usually containing a single dose of active ingredient'.

According to USP24 capsules are 'solid dosage forms in which the active ingredients are sealed in a hard or soft container or shell'. BP defines capsules as 'solid preparation with hard soft shells, of various size, shapes and capacities, containing a single dosage of active ingredient'.

(b) Advantages of Capsules:

1. Capsules are tasteless, odourless and are readily identifiable.
2. They are elegant, attractive in appearance and are comparatively cheaper.

3. Drugs with unpleasant odour or taste can be administered as capsule.
4. Capsules can be filled instantly and congenitally.
5. Physicians have freedom to manipulate the dose for individual patient.
6. Capsule is too easy to handle and carry in ambient environment.
7. They are easily swallowed and quickly dissolved in the stomach.
8. Capsule shells have little or no interaction with GI contents.

(c) Disadvantages of Capsules:

1. Capsules are more expensive than tablets.
2. Some hygroscopic drugs absorb moisture from the capsule shell making it more brittle.
3. Capsules are not air tight thus the shelf life is shorter.
4. Unsuitable for concentrated solutions that require dilution prior to encapsulation.
5. Filling operation is performed without compression and thus occupies more volume.
6. Capsule filling volumes are limited thus limits the dose of the drug.

(d) Classification of Capsules:

Capsules are classified into two main types as:

1. Hard gelatin capsules (HGC)
2. Soft gelatin capsules (SGC)

5.2.1 Hard Gelatin Capsules

James Murdock of London patented the two-piece telescoping gelatin capsule in 1847. HGC are made in two parts by dipping metal pins in the gelling agent solution. Before use, the two halves are separated, the capsule is filled with powder or more normally pellets and the other half of the capsule is pressed on. With the compressed slug method, weight varies less between capsules. However, the machinery required to manufacture them is more complex. In principle, any type of formulation may be dosed into hard capsules, from blends or granules, to coated pellets, to other oral dosage forms such as tablets, micro-tablets, smaller capsules, to semisolids and pastes. It is also possible to fill liquids, provided that the material of the capsule is not soluble in the solvent used in the formulation, for example, Liquid Balsam Copaivae.

(a) Primary ingredients in HGC:

The HGC composition consists of gelatin, plasticizer and other components.

Gelatin: Gelatin is a protein almost soluble in all polar solvents that can behave as a gelling agent in manufacturing. It is a mixture of peptides and proteins produced by partial hydrolysis of collagen. Pork skin is commonly used as the raw material due to its unique ingestion and dietary criteria but for specialized applications beef skin and crushed bone can also be used. There are two basic types of gelatins. Type A is derived from acid treated precursor that exhibits an iso-electric point at pH 9. It is manufactured mainly from pork skin. Type B is derived from alkali treated precursor that exhibits an iso-electric point at

pH 4.7. It is manufactured mainly from animal bones. It contains up to 15% glutamic acid (an antibiotic) as a preservative. Gelatin melts upon heating but solidifies once cooled and with water it forms a semi-solid colloid gel. Its gel exists over only a narrow temperature range.

Plasticizers: Plasticizers are additives that increase the plasticity or fluidity of a material. It provides structural integrity to the gelatin so the capsule can maintain its shape. The amount of plasticizers determines the rubbery texture of the capsule. Sorbitol and glycerin are the most commonly used plasticizers in HGC.

Other components: Other components of HGC are colouring agents, preservatives such as methyl paraben, lubricants such as stearic acid and surface treatment agents. In addition, various colouring agents such as soluble synthetic dyes (coal tar dyes) and insoluble pigments are used for identifying the product as well as for improving patient compliance, for example, white for analgesia; lavender for hallucinogenic effects; orange or yellow for stimulants and antidepressants drugs. Titanium dioxide (TiO_2) may also be included for opacifying effects. Opaque capsules are used to provide protection against light or to conceal the contents.

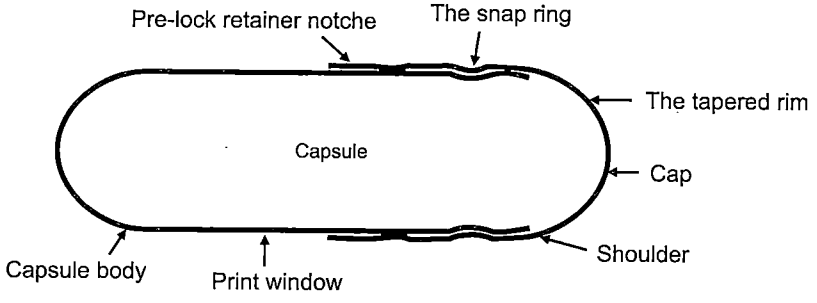


Fig. 5.1: Parts of Hard Gelatin Capsule

(b) Manufacture of HGC:

The major component of HGC is gelatin. The basic processing operations involved in gelatin preparation are presented in Fig. 5.2. Gelatin manufacturing involves organic reactions and thus its preparation is a time consuming process and may require many weeks to complete the processing. Previously gelatin capsules were fabricated by pharmaceutical manufacturers but currently, capsule shell production is done by third party suppliers.

Gelatin solution: Capsule production is an automated operation that begins with solubilizing the dry gelatin with a mixture of plasticizer and purified water. The gelatin solution is heated and transferred to a dip pan or pot which holds specific amount of hot gelatin at particular temperature. The amount of gelatin in pot is maintained automatically by controlling flow from hopper.

Dipping: In this process, stainless steel pins are submersed in the heated gelatin solution to simultaneously form caps and bodies. The pins are maintained at 20 - 22 °C; whereas the dipping solution is maintained at 50 °C in a heated, jacketed dipping pan. The length of time to cast the film is about 12 sec. During production, the thickness of the capsule wall is controlled by the viscosity of the gelatin solution, speed and time of dipping.

Spinning: After dipping, pins are elevated and spinned to uniformly distribute the gelatin over the surface to avoid the formation of a bead at the capsule ends. This operation is performed until pins are facing upward.

Drying: Blasts of cool air, which dry and solidify the capsules, is the next operation. The viscous gelatin is allowed to dry on the pins (about 100 pairs of pins/mould) and when dry these are removed from the pins.

Stripping: A series of bronze jaws are used to strip the cap and body parts of the capsules from the pins. Capsules are rotated on a fixed clamping device to keep them in place.

Trimming: Once the capsules are dry, they are separated from the pins by a set of mechanical jaws. The stripped cap and body parts are further trimmed to the required length using stationary knives. The stripped cap and body parts are delivered to a collector where they are firmly held together. As collector rotate, knives trims shells to the required length.

Joining: After trimming to the right length, the cap and body are aligned concentrically in channels and the two portions are slowly pushed together to join them. The joined whole empty capsule is ejected from the machine.

Polishing: Empty capsules are polished in pan. Acela-cota pan is used to de-dust and polish. Capsules are rubbed with cloth to make surface smooth.

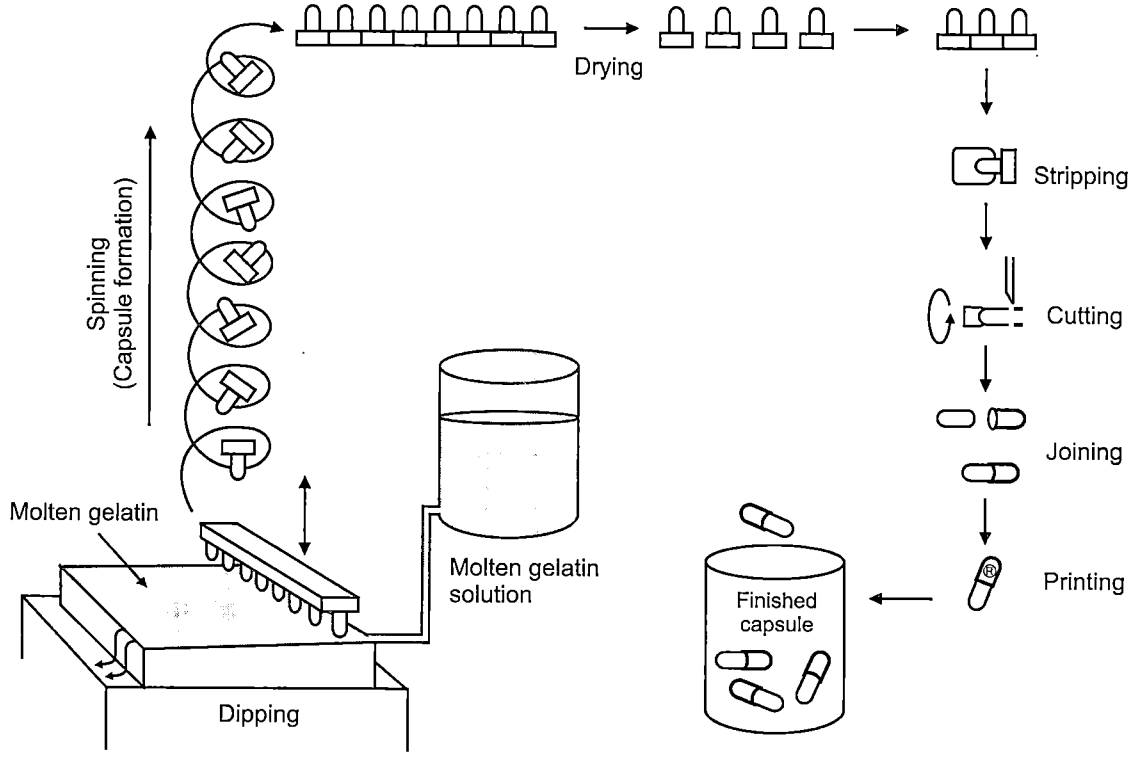


Fig. 5.2: Steps in Production of Empty Hard Gelatin Capsule

Brushing: Capsules are fed under soft rotating brush to make them free from adsorbed particles.

Sorting: The capsules moving on conveyor are examined visually for sorting defective units by the automated systems or by inspectors.

Printing: Often capsules are printed before filling operation. Printing is done on offset rotary printing machines having capacities of about 7.5 to 8 lakh capsules per hour.

(c) Size of Capsules:

Capsule consists of a base or body and a shorter cap, which fits firmly over its body (base). Empty HGC are made in a variety of sizes. For human use, eight sizes of capsules are available. The capacity of capsule varies from 0.13 mL to 28 mL. Some types of hard gelatin capsules have a locking cap, which makes it more difficult to reopen. For human use, empty capsules ranging in size from 000 (largest) to 5 (smallest) are used, Fig. 5.2 (a). Generally, capsules encapsulate ingredients between 65 mg to 1 g. For veterinary use size no. 10, 11 and 12 with capacities of 30, 15 and 7.5 g, respectively, are used, Fig. 5.2 (b).

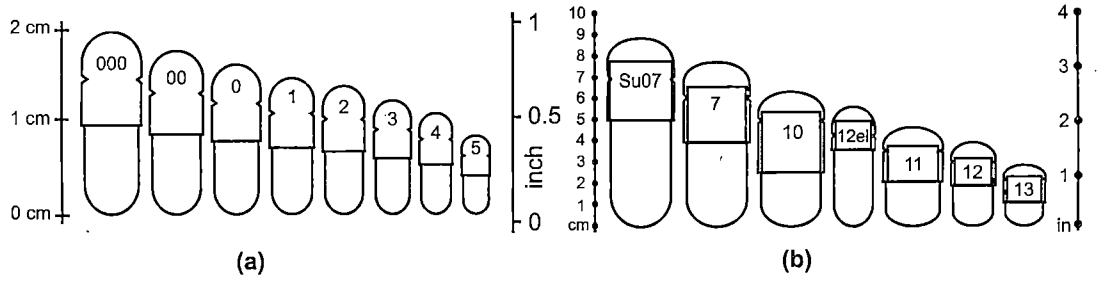


Fig. 5.3: Relative size of capsule for (a) human use and (b) animal (veterinary) use

(d) Shape of Capsules:

The standard HGC come in traditional, symmetrical bullet or cylindrical shapes. Capsules are either dot sealed or banded to prevent body and cap separation after filling. As an alternative and to achieve other functionalities self-locking capsules are manufactured, for example, coni-snap and snap fit by Park-Davis, Lo-cap as Posilok by Eli Lily and Star-Lok and Lox-It by Scherer. Other shapes include pulvule tapers to a bluntly pointed end and spansule capsules taper at both the cap and body ends.

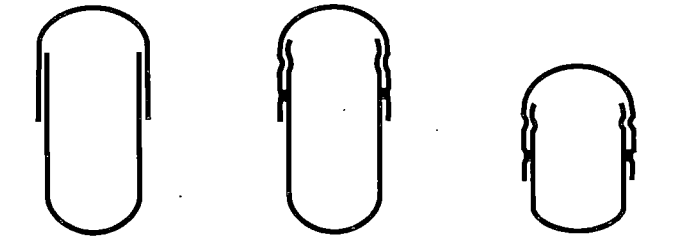


Fig. 5.4: Shapes of Capsules

(e) Filling:

Capsule filling is a complex process. The capsule filling process may vary depending on filling operation selected, for example, hand operated or bench scale capsule filling, semi-automatic capsule filling, fully automatic capsule filling machine, etc. The HGC can be filled using manual, semi-automatic and automatic capsule filling machines. The choice of capsule size and fill weight depends upon the unit dose requirements and the formulation to be filled. The product to be encapsulated must be well developed to ensure mass uniformity.

(i) Manual Filling: The manual filling methods are as follows:

(1) Punch method: In this method precise number and size of capsule to be filled is selected. Capsules body and cap is separated. The powder or granules to be filled are taken on a piece of clean paper and filled by holding the capsule body in between thumb and forefinger. It is a common technique used by pharmacist but is a slow and laborious.

(2) Volume fill method: This method is based upon the total amount of drug needed based upon the amount per dose per day and total number of dosing days.

(3) Tamping method: This method involves compression of contents. The majority of high speed filling machines does capsule filling using tamping method.

(4) Wax fill method: This method involves traditional steps of melting wax and mixing of the drugs followed by filling the capsules similar to punch method.

(ii) Machine Filling: Hand filling of small quantities of capsules is employed for small volume fills for controlled drug substances and to minimize and more readily account for product losses. For larger quantities up to 3000 capsules/min, automated capsule filling machines are most commonly used.

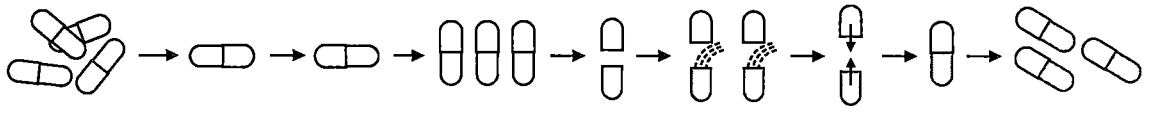


Fig. 5.5: Process of filling hard gelatin capsule

In filling HGC with powders, the machine used performs basically four operations. The sequence of operation is rectification of the capsules, separation of the body from the cap, filling capsule body with powders and replacement of the cap. Techniques of filling powders into the capsules vary greatly from manufacturer to manufacturer. The basic operation in filling HGCs is presented in Fig. 5.5. Special techniques used for pellet, tablet, semi-solid and liquid filling for commercial productions include plate method, auger fill method, dosator feed method, dosing disc and tamping finger method, vacuum filling (Accofil) and fluidizer method.

Finishing: Capsules are sealed and reshaped if required using Etaseal process. This thermal welding process forms an indented ring around the waist of the capsule where the cap overlaps the body. On a small scale, capsules are cleaned individually by rubbing them

with a clean gauze or cloth. On a commercial large scale, capsule-filling machines are affixed with a cleaning vacuum that removes any extraneous material from the capsule surfaces as they exit the equipment.

(f) Manufacturing defects:

The capsule should be prefect with respect to its shape, size, appearance, colour, texture, taste, and odour. The body and cap of gelatin capsules are susceptible to several common flaws which are caused by inconsistent manufacturing process. In the manufacturing of HGC during operations few defects are developed. Major defects include hard shell formation, cracks, breaks, pinholes or splits, loss of integrity, colour variation, non-uniformity of appearance, surface spots and embedded particles on capsules, non-uniform body and cap, improper fitting, false odour, empty capsule, foreign matter inside the capsules, improper filling etc. Whereas minor defects are pits, dents, thin area, specks, spots or blemishes, rough surface with adhering spots, improper opacity, etc.

Storage of Hard Gelatin Capsule:

HGC must be protected against excessive heat and humidity. Recommended storage conditions for empty HGC are 15 to 25 °C and a relative humidity (RH) of 35 - 65%. This condition is designed to minimize moisture absorption or loss, and the resultant changes in physical dimensions, during the encapsulation operation. Cartons containing empty capsules must be sealed and bags should never be left open in areas where the air is not controlled. Generally, capsules are packed in strong heavy wall corrugated boxes with 100 micron non-static polyethylene bags, sealed by heat. During transportation, the finished HGC must be stored at moisture content of 13 - 16% with 50% RH at 21 °C. HGC are stored away from direct sunlight, hot water/air radiators, hot water pipes, under water pipes and steam pipes.

5.2.2 Soft Gelatin Capsules

SGC, also known as softgels, consist of one-piece hermetically-sealed soft shells. These capsules were developed in the 19th century to mask unpleasant taste and odour of drugs. It encapsulates non-aqueous liquids, suspensions, semisolid or pasty materials, or dry powders. Their special application is to deliver volatile drug substances or drugs susceptible to deterioration in the presence of air. Softgel shows highest content uniformity of low-dose drugs and has consumer preference due to its easy swallowing feature. The softgel offers delivery of a poorly soluble liquid matrix designed to solubilize rapidly to improve oral bioavailability. The softgels are suitable for non-aqueous solutions and are known to melt within a few minutes in the stomach.

(a) Nature of Shell and Capsule Content:

(i) Soft gelatin capsule: The SGC shell is composed of gelatin, plasticizer and water. It also contains additional ingredients like preservative, colouring agent and opacifying agent, etc. The basic component of soft gelatin shell is gelatin. Its unique oxygen impermeability and the combination of film forming capability and thermoreversible sol/gel transformation

favour its use for the capsule production. The residual shell moisture content of finished SGC is in the range of 6-10%. Sugar up to 5% may be included to give a "chewable" quality to the shell. Iron is always present in the raw gelatin and its concentration is usually not more than 15 ppm. Iron has effects on FD&C certified dyes and possible colour reactions with organic compounds. The ratio of dry plasticizer to dry gelatin can vary from 0.3 - 1.0 for very hard shell to 1.0-1.8 for very soft shell.

(ii) Soft starch capsule: Various starches can be used to make soft shell capsules. Moisture content in starch capsule lies between 12 - 14% w/w and more than 50% is tightly bound to starch. The high level of moisture in starch capsules provide better stability and reduce susceptibility to changes on storage. Starch capsules show pH independent dissolution similar to those of soft gelatin capsules. The major advantage of starch capsules is its readiness for filling immediately after manufacturing. In addition, it offers greater resistance to humidity and heat than gelatin and allow easy filling as they are non-static. It has good surface finish and its coating is less problematic due to its smooth seal and higher bulk density of the contents.

(b) Primary ingredients in SGC:

Plasticizers: Plasticizers are used in the range of 20-30% to make the softgel shell elastic and pliable. The most commonly used plasticizer is glycerin but frequently sorbitol and PEG 400 are also used in combination with glycerin.

Water: Water is essential component of the soft gel shell that ensures proper processing during gel preparation and softgel encapsulation. It usually accounts for 30 - 40% of the wet gel formulation.

Colourants and/or Opacifiers: Colourants can be either natural or synthetic, and are used for product elegance and identification. Opacifier is added when the fill formulation is a suspension or to prevent photodecomposition of light-sensitive fill matrix ingredients. For example, titanium dioxide produces an opaque shell.

Preservatives: Preservatives are incorporated to preserve the drug medicament from the microbes. Methyl paraben and propyl paraben up to 0.2% of the total drug are commonly used.

Flavouring agents: Flavouring agents are used to mask the taste of formulation components. The commonly used flavouring agents are ethyl vanillin and essential oils whereas sweetening agents such as various sugars, especially sucrose is also used.

(c) Size and Shapes:

SGC are soft, elastic and are one piece hermetically sealed. These are available in different shapes and sizes such as spherical, cylindrical, oval, elliptical, oblong and special tube shapes with and without twist off. The spherical capsules are called pearls. The content in soft gelatin capsules varies from 0.1 to 30 mL.

Fig. 5.6: Various Shapes of Soft Gelatin Capsules

(d) Base Adsorption and Minim/Gram Factors:

Base adsorption and minim per gram factor is determined when the SGC shell contains suspension.

(i) Base adsorption: It is crucial to find minimum quantity of base (inert liquid or vehicle) required to prepare the suspension. Base adsorption is defined as the minimum amount of base or vehicle in grams required per gram of solid drug to form a mixture which easily can be encapsulated in soft gelatin capsule.

$$\text{Base adsorption} = \frac{\text{Weight of base (g)}}{\text{Weight of drug (g)}} \quad \ldots (5.1)$$

It is a unit less value as both parameters are in grams.

(ii) Minim per gram factor: The minim per gram factor is the volume in minims that is occupied by one gram (S) of the solid plus the weight of the liquid base (BA) required in producing a mixture which can be encapsulated.

$$\text{M/g factor} = BA + S \div (W/V) \quad \ldots (5.2)$$

Where, BA is base adsorption, S is solid drug, W is weight and V is volume in minims. The ratio W/V is density of the mixture.

For example, M/g = 50 meaning 1 g drug in a mixture occupies 50 minims (since 1 mL = 16.23 minims, 50 minims = 3.06 mL).

(e) Production of SGC:

SGC are manufactured by five methods namely; plate process, rotary die process, reciprocating die process, accogel process and as a seamless gelatin capsules. SGC compared to HGC contain more moisture and are prone to microbial decomposition. Gelatin used for making SGC is obtained from the bone and skin of animals that has bloom strength of 150 – 175 g. All operations of the SGC production take place simultaneously with filling step as the most challenging process.

(f) Finishing of Softgels:

After drying, softgels are sorted, polished, printed, and inspected for their quality. The finished softgels are then packed into suitable containers, typically of low density polyethylene (LDPE) bags, high density polyethylene (HDPE) bottles, or blisters.

(g) Storage of SGC:

SGC generally contain the medicament dissolved or dispersed in oils or lipophilic liquids. The inherent flexibility of the softgel capsule is due to the presence of plasticizers and residual moisture in the capsule shell. The atmospheric moisture may permeate into the

capsule shell or into the fill liquid. The drug or fill liquid may migrate into the capsule shell, while the plasticizer or residual water in the gelatin shell can potentially migrate into the fill. Volatile components in SGC may escape into the atmosphere. Therefore, recommended storage conditions for the HGC include a temperature range of 15 – 30 °C and a RH of not more than 50%. When stored under these conditions, the equilibrium moisture content of the shell material and oxygen permeability through the material are minimal, thus improving the stability of the softgel products.

(h) Quality Control Tests:

(1) Size and shape: This test encompasses testing capsules for uniformity of size and shape and compared with the standard.

(2) Unique identification markings: Capsule surfaces may bear symbols or other unique identification markings, for example, white cap, red body, imprinted with "Rx" on cap, etc., for better identification. Inspecting capsule for these features is part of this test. If defective capsules are found, are rejected.

(3) Moisture permeation: The degree and rate of moisture penetration are determined by packaging the dosage unit together with a colour revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for colour change. Any change in colour indicates absorption of moisture. By measuring pretest weight and protest weight of pellet, the amount of moisture permeated is calculated.

(4) Content uniformity test: According to BP the content of the active ingredient in each of 10 capsules is taken at random using the method given in the monograph or by any other suitable analytical method of equivalent accuracy and precision.

(5) Uniformity of mass: The intact 20 capsules are weighed. Individual capsule is opened without losing any part of its shell and the contents are completely removed. The weight of the contents is the difference between the initial weight and the weight of shell.

(6) Disintegration test: To test for disintegration time, one capsule is placed in each tube of disintegration test apparatus. Capsules comply with the test, if disintegrate, and all particles pass through the 10-mesh screen within the time specified.

(7) Dissolution test: The USP or BP dissolution test apparatus (Basket type) is used to determine amount of drug released. A single capsule is placed in the apparatus, and the apparatus is operated at the specified rate. Within the specified time interval, or at each of the times stated, a specimen sample is withdrawn and analyzed using a suitable assay method as directed in the individual monograph.

5.3 LIQUID ORAL PREPARATIONS

The liquid oral preparations are dosage forms of a drug for administration by oral route. These preparations are classified as monophasic and polyphasic liquid dosage forms. Monophasic liquid dosage forms are true or colloidal solutions. The component of the solution which is present in a large quantity is solvent and the component present in a small quantity is a solute. Water is commonly used as solvent for majority of monophasic liquid dosage forms. A solution is homogenous because the solute is in an ionic or molecular form of subdivision.

Liquid dosage forms can be formulated as solutions, suspensions and emulsions depending on the nature of the drug, its solubility and stability. Emulsions and suspensions are heterogeneous. They may also be formulated as ready to use liquids and powders for reconstitution into liquids. These dosage forms are generally used in geriatric and paediatric patients. They need various excipients including vehicle, stabilizer, and viscosity builder, preservatives, sweeteners, colour and flavour. In addition, solubilizers are required for clear liquids; suspending agents for suspensions and emulsifying agents for emulsions. The most common forms of liquid dosage form are syrups, suspensions and elixirs. Liquid forms are sometimes referred as vehicle which delivers the active drug.

Advantages:

1. Liquids oral preparations are pourable and have faster absorption and rapid action.
2. They are more flexible to achieve proper dosage of the medication.
3. These are used fairly commonly by young children or the elders who have trouble swallowing the solid oral dosage forms.
4. The products like adsorbents and antacids are more effective in liquid dosage forms.
5. They can be measured with ease using measuring device provided with the package.
6. They can be easily flavoured, coloured or sweetened.
7. They are the only alternatives for certain drugs such as castor oil.

Disadvantages:

1. Oral liquid dosage forms usually have shorter shelf life.
2. These are much difficult to administer and have special storage requirements.
3. They have less dosage accuracy.
4. Problem occurs in preservation of liquids oral preparations.
5. Being bulky its transportation is difficult.
6. They are difficult to recover once lost due to spillage or breakage of the container.

5.3.1 Solution

(a) Definition:

A solution is a homogenous liquid dosage form prepared by dissolving active ingredient(s) in an aqueous or non-aqueous solvent.

(b) Classification:

(i) According to composition and uses:

(a) Syrup: Aqueous solution containing sugar.

(b) Elixir: Sweeten hydro-alcoholic solution.

(c) Spirit: Solution of aromatic materials in alcohol.

(d) Aromatic water: Solution of aromatic materials in water.

(e) Tincture: Solution prepared by extracting constituents from crude drugs.

(f) Injection: It is prepared to be sterile and pyrogen free intended for parentral administration.

(ii) According to vehicle:

(a) Aqueous solutions: Solutions that contains water as solvent, for example, sugar in water.

(b) Non-aqueous solutions: Solutions that contain solvent other than water, for example, ethanol and ethyl ether (topical protective).

Solutions can also be classified as:

(i) Concentrated and dilute solution: The solution with greater proportion of solute is called concentrated solution; whereas solution with less proportion of solute is called dilute solution. Examples: Concentrated Almond Extract, Dilute Ammonia Solution.

(ii) Saturated solution: A solution in which no more solute can be dissolved at given temperature is called saturated solution. Example: Simple Syrup IP.

(iii) Unsaturated solution: A solution in which more solute can be dissolved at given temperature is called unsaturated solution. Example: Aqueous Iodine Solution.

(c) Advantages of Solutions:

1. Solutions being liquids; are easier to swallow and therefore suitable for children, old aged and unconscious people.
2. Doses can be easily adjusted based upon need.
3. A drug in solution is at molecular level and thus it can be absorbed rapidly and become more quickly effective.
4. A solution being a homogenous system uniform dose can be withdrawn.
5. The drug is uniformly distributed throughout the solution.

6. Drugs in solid state can irritate the gastric mucosa if localized in one area. Thus, irritation is reduced by administration of such drugs as a solution.

(d) Disadvantages of Solutions:

1. Solutions are bulky and inconvenient to transport and store.
2. The stability of ingredients in aqueous solution is often poor.
3. Solutions are susceptible to microbial growth and thus may require preservatives.
4. Accurate dose measuring depends on the ability of patient to measure the dose.
5. Solutions need measuring device to accurately measure the dose.
6. Stability of some drugs in aqueous solvent is much less.
7. The maximum possible concentration of drug in solution varies greatly.

(e) Formulation of Solution:

Ferrous Sulphate Mixture Paediatric B.P.C.

Ingredients	Quantity	Use
Ferrous sulphate	1.2 g	Iron supplement
Ascorbic acid	0.1 g	Antioxidant
Orange syrup	10 mL	Sweetening agent
Chloroform water (DS)	50 mL	Preservative
Purified water q.s. to make	100 mL	Vehicle

Method of Preparation:

This solution is prepared by dissolving ferrous sulphate in 10 mL water and then chloroform water, ascorbic acid and orange syrup is added. The solution is filtered and final volume is adjusted.

Use: To treat iron deficiency.

(f) Storage of Solutions:

Solutions for oral use are usually packaged in plain or amber medicine bottles, with a re-closable child-resistant closure with some exceptions. These are stored in cool and dry place away from light. Solution preparations containing photosensitive constituents must be packaged in amber coloured bottles. During storage care must be taken to ensure preservation of the drug(s), as well as effective prevention of microbial contamination. The solution should not undergo dilution at any point in the supply chain, unless recommended. Oral solutions stored for any period should be regularly re-assessed for potency and stability, prior to administration. An expiry date should appear on the label for extemporaneously prepared solution preparations.

(g) Quality Control Tests:

(1) General tests: Evaluation of solution preparation for visual appearance, colour, taste, odour, labeling, and homogeneity.

(2) Identification tests: Solution preparation is tested for physico-chemical tests for identification.

(3) Assay: Solution preparation is assayed using titrimetry, colorimetry or UV-spectrophotometry methods to estimate percent drug content.

(4) Pourability: It is adaptability to being poured. Solution preparations are tested to determine pourability by measuring the flow time and flow rate.

(5) Viscosity: Viscosity of solution preparation is determined using various viscometers *viz.* Ostwald's viscometer, Brookfield viscometer, etc.

(6) Clarity: A liquid is considered clear if its clarity is the same as that of water or of the solvent used for preparing the solution under examination or if its opalescence is not more than that of opalescence standard (OS). Clarity of solution preparation can also be determined using clarity test apparatus.

(7) Crystallization and precipitation: Different solution preparations have different critical limits of supersaturation, above which spontaneous nucleation begins. Below this limit there is no nucleation, but only crystal growth. Supersaturation is employed to test crystallization and precipitation process.

(8) Gas evolution: Gas chromatography is used to determine evolution of gas from the solution preparation.

(9) Relative density: It is the density of solution preparation in relation to reference standard. Pycnometer or density bottle is used to determine density of solution.

(10) pH: The simplest and cheapest method to determine pH is to dip a piece of pH paper into the syrup. The paper is impregnated with chemicals that change colour and the colour may be compared to a chart supplied with the paper to give the pH of the sample. If greater accuracy is required a pH meter is used. A typical pH meter measures and displays the pH reading.

(11) Surface tension: Surface tension of solution is a physical property determined using various instruments such as stalagmometer.

(12) Microbial limit test: Microbial contamination is determined by the total viable aerobic count, which is the sum of the bacterial count and the fungal count. Membrane filtration, plate count methods and most probable-number method are used. According to IP the acceptance limit for this is not more than 103 bacteria and not more than 102 fungi per gram or mL of the preparation. Test for specified microorganisms such as Escherichia coli contamination is also performed.

(13) Stability: Solution preparations can be tested for short-term and long-term durations against different temperature, light and humidity conditions.

(14) Container and closure compatibility: Compatibility is tested based upon container and closure material and their specifications as per official compendia.

5.3.2 Syrup

(a) Definition:

Syrup is a highly concentrated, aqueous solution of sugar or a sugar substitute that traditionally contain a flavouring agent. The strength of sugar in syrup is 66.7 %w/w. The syrup is usually used as a flavoured vehicle for drugs. It also masks the taste of bitter substances in the formulation.

(b) Classification:

(1) Simple syrup: Simple Syrup I.P. is 66.7% w/w sucrose solution in water prepared by simple solution method. In simple syrup USP sucrose at the concentration of 85% w/v is dissolved in water. Syrup is protected from bacterial contamination by virtue of its high solute concentration. More dilute syrups are good media for microbial growth and require the addition of preservatives. Syrups being saturated solutions of sucrose in water exert high osmotic pressure and thus no free water is available for microbial growth. Hence, preservative is not required to be added in simple syrup.

Examples: Simple Syrup I.P., Simple Syrup U.S.P., Simple Syrup B.P.

The USP simple syrup is 85%w/v (65% w/w) sucrose solution with a specific gravity of 1.313 whereas BP simple syrup is 87.5% w/v (66.7% w/w) of sucrose as the solute in 33.3% w/w of water. The USP syrup is prepared by dissolving 850 g sucrose and enough distilled water to make 1000 mL. The BP syrup is 865 g – 875 g sucrose and enough distilled water to make 1000 mL.

(2) Medicated syrup: Medicated syrup is nearly saturated solution of sugar in water in which drug is dissolved. These syrups contain medicinal substances giving them therapeutic value. Some of these syrups are used as cathartic, cholinergic, decongestant, expectorant, fecal softener, sedative, etc.

Examples: Meperidine HCl Syrup (Demerol®), Dicyclomine HCl Syrup (Bentyl®), Oxybutynin Chloride (Ditropan®), Chlorpromazine HCl Syrup (Thorazine®), etc.

(3) Non-medicated or flavoured syrup: These syrups do not contain drug, instead they consist of various aromatic and pleasantly flavoured substances and is intended as a vehicle or flavour for preparations.

Examples: Cherry Syrup, Orange Syrup, Cocoa Syrup, etc.

(4) Artificial syrup: Artificial syrup is prepared from polyols such as sorbitol, glycerin, propylene glycol or cellulose polymers such as methyl cellulose, hydroxy methyl cellulose and artificial sweeteners such as sodium saccharine, sodium cyclamate, aspartame, etc. Artificial sweeteners are almost 500 times sweeter than sucrose. They are non-caloric and they do not elevate the blood glucose level thus used in diabetic patient medications.

(c) Advantages of Syrup:

1. Syrups have ability to disguise bad taste of drug to administer easily to children.
2. Thick character of syrup has soothing effect on irritated tissues of throat.
3. Syrups do not contain alcohol as preservative.
4. Most syrup is inherently resistant to microbial growth.
5. Syrups are attractive and popular amongst youngsters.
6. Because of its high viscosity it exhibits mouth feel qualities.
7. These are widely acceptable due to the wide variety of flavours used.

(d) Disadvantages of Syrup:

1. Patients who have to consume food having low calories should be aware of amount of sugar present in syrup.
2. Patient taking syrups regularly are at the risk of dental carries.
3. It is not suitable for diabetic and paediatric patients due to presence of sugar and alcohol, respectively.
4. Crystallization of sugar takes place if is container is left open.

(e) Methods of Preparation:

Syrups are prepared by any of the following methods, depending upon the physical and chemical characteristics of the ingredients:

(i) Solution with the aid of heat: Sugar is added to the purified water and heated until it dissolves. Then, the other required heat-stable components are added to the hot syrup, the mixture is cooled and its volume is adjusted by the addition of purified water. The use of heat facilitates the rapid solubilization of the sugar and other components of syrups. If excessive heating occurs, then sucrose may be hydrolyzed into dextrose and fructose. This hydrolytic reaction is called sugar inversion, and the combination of the two monosaccharides is known as invert sugar. Invert sugar is colourless and sweeter than sucrose. Syrup darkens due to the effect of an overheating of fructose. When the syrup is overheated, it becomes amber-coloured due to the caramelization of the sucrose.

(ii) Solution by agitation: Sucrose and other ingredients are dissolved in purified water. Usually vessel of greater capacity than the volume of syrup is used to permit thorough agitation of the mixture.

(iii) Addition of sucrose to a medicated liquid or to a flavoured liquid: Medicated liquid such as a tincture or fluid extract is the active ingredient in the preparation of syrup. If the extract contains alcohol-soluble ingredients and the amount of alcohol is high, then sucrose is added directly and stirred. If the alcohol content is low and all the ingredients are water-soluble, then the liquid extract is directly mixed with the prepared syrup.

(iv) Preparation of syrup by percolation: Purified water is added slowly to a bed of crystalline sucrose, thereby dissolving it and forming the syrup. If needed, a portion of the percolate is recycled.

(f) Formulation of Syrup:

Ephedrine Sulfate Syrup

Ingredients	Quantity	Use
Ephedrine sulfate	4 g	Decongestant
Citric acid	1 g	Antioxidant
Amaranth solution	4 mL	Colouring agent
Caramel	0.4 g	Flavouring agent
Lemon oil	0.125 mL	Flavouring agent
Orange oil	0.25 mL	Flavouring agent
Alcohol	25 mL	Preservative
Sucrose	800 g	Sweetening agent
Purified water, q.s. to make	1000 mL	Vehicle

Method of Preparation:

Syrups are carefully prepared in clean equipment to prevent contamination. Preparation of syrup depends on the physical and chemical characteristics of the substance employed for its preparation. Methods that are commonly used for preparation of syrups include agitation without heat, solution with heat, addition of a medicated liquid, percolation and reconstitution.

Use: To treat cough.

(g) Storage of Syrup:

Syrups are preserved in tight, light-resistant containers, avoiding exposure to excessive heat and moisture until it is opened, and then it must be stored in a refrigerator till its complete consumption. Overall, syrups containing stable drugs are stored at 25 –27 °C and those containing thermolabile drugs are stored at 4–5 °C in refrigerator.

(h) Quality Control Tests:

(1) **Visual inspection:** With visual inspection, the ingredients and the final products are carefully examined for purity and for appearance. It should be good looking and elegant in appearance.

(2) **Cap locking:** The syrup is placed in 60 mL bottles, and the bottles are turned upside down. The bottle opening manner is evaluated after one week. Cap locking would be confirmed in case the cap could not be easily opened.

(3) **Crystallization and precipitation:** Supersaturation is employed to test crystallization and precipitation process. The syrup is placed in a refrigerator for a week and is examined for any precipitate afterwards.

(4) **Light transmittance**: A light transmittance meter is used to check syrup colour. A syrup sample is checked for colour by passing light through the sample. The percent of light transmission is compared to light transmission rates set for different grades.

(5) **Sucrose concentration:** If the concentration of sucrose in the syrup is very high it may crystallize the syrup and thus low sucrose concentrations may favor the microbial growth. There is no specific method for the determination of sucrose in syrup, but one can use HPLC and UV-spectroscopy for this purpose.

(6) **pH:** The pH of solution preparation can be determined using pH paper or pH meter.

(7) **Physical stability:** The syrups must be stable physically, for example, must comply for its appearance (no crystallization and microbial growth), colouring agents used must be completely soluble and must be palatable (odour and taste).

Identification, assay, pourability, viscosity, relative density and clarity or opalescence and microbial limit tests are preformed similar to solution preparations.

5.3.3 Elixir

(a) Definition:

The USP XVII defines elixirs as a clear, sweetened hydro-alcoholic liquid intended for oral use containing flavouring substances or active medicinal agents.

The primary solvents in elixirs are alcohol and water, with glycerin, sorbitol and syrup sometimes as an additional solvent and/or sweetening agents. They are prepared by simple solution or admixture of the several ingredients. They are used either as vehicles or for the therapeutic effect of the medicinal substances that they contain.

(b) Classification:

1. **Flavoured elixirs:** These are used for flavouring purpose and as vehicles in other liquid preparations for oral use. Example: Aromatic Elixir U.S.P.
2. **Medicated elixirs:** These are used for therapeutic purpose or as vehicles for other drugs. Examples: Dexamethasone Elixir U.S.P., Phenobarbital Elixir U.S.P. etc.
3. **Dry elixirs:** Dry elixirs are the formulations in which drug and alcohol are encapsulated in dextrin to enhance the solubility and so the drug bioavailability. Examples: Dexibuprofen Dry Elixir, Nifedipine Dry Elixir, etc.

(c) Advantages of Elixirs:

1. Elixirs maintain both water-soluble and alcohol-soluble components in solution.
2. They are more stable because of self preservation property.
3. They are easily prepared by simple solution method.
4. They are used as vehicle and for dilution of medicated elixirs.
5. They are good at masking taste of bitter drugs and excipients.
6. Elixirs have low viscosity and thus flow more freely.
7. These are flexible and easy to administer to patients having swallowing problems.

(d) Disadvantages of Elixirs:

1. Less effective than syrups in masking taste of medicated substances.
2. Contains alcohol that accentuates saline taste of bromides as well as they can be nasty to children and adults who avoid alcohol.
3. As syrups contain volatile components, they need to be stored in airtight containers to prevent losses.
4. They should not be stored in the vicinity of heat source.

(e) Formulation of Elixir:

Aromatic Elixir USP

Ingredients	Quantity	Use
Compound Orange Spirit	12 mL	Flavour
Syrup	375 mL	Sweetener
Talc	30 g	Adsorbent
Alcohol and Purified water q.s.to make	1000 mL	Vehicle

Method of Preparation:

Add sufficient quantity of alcohol to the compound orange spirit to make 250 mL. Add to this the syrup in several portions, agitating vigorously after each addition and then add in the same manner, the required quantity of purified water. Mix the talc with the liquid and filter through a filter wetted with diluted alcohol, returning the filtrate until a clear liquid is obtained. Compound Orange Spirit in this formulation is used to ensure a uniform proportion of the several oils (i.e. orange, lemon, coriander, and anise), in every lot of the elixir. The alcoholic solution also preserves the delicate flavours of orange and lemon for a considerable time.

Use: Pleasantly flavoured vehicle in the preparation of many medicated elixirs.

(f) Storage of Elixirs:

Similar to syrups, elixirs are also preserved in tightly closed, light-resistant containers, avoiding exposure to excessive heat, light and moisture until it is opened, and in some cases it must be stored in a refrigerator till its consumption. Elixir preparation under use must be properly closed after withdrawal of dose and stored at places that prevent environmental effects, away from children.

(g) Quality Control Tests:

(1) Sucrose concentration: There is no specific method for the determination of sucrose in syrup, but one can use HPLC and UV-spectroscopy for this purpose.

(2) Alcohol content: The quantitative determination of alcohol is performed using distillation method unless otherwise specified in the individual monograph. The amount of alcohol in preparation headspace in a container is determined by gas chromatography.

(3) Refractive index: The refractive index of elixirs is determined by using Abbe's refractometer. It should be in the range of 1.4608 to 1.4630.

Other quality control tests used include visual inspection, consistence, identification, assay, pourability, viscosity, relative density, pH, clarity or opalescence, cap locking, crystallization and precipitation, light transmittance, microbial limit and physical stability similar to the solution and syrup preparations.

5.3.4 Emulsion

(a) Definition:

An emulsion is biphasic liquid system in which one liquid is dispersed throughout another liquid in the form of small droplets and the system is stabilized by third substance called emulsifying agent (emulsifier).

Emulsions are thermodynamically unstable and thus, the emulsifier is added to stabilize the system. The emulsifier prevents coalescence, the merging of small droplets into larger droplets and into individual separated phases. These agents form a thin film around the globules of dispersed phase. The dispersed phase or the continuous phase may vary in consistency from a mobile liquid to semisolid. Thus, pharmaceutical emulsions range from simple emulsion (low viscosity) to creams and ointments (high viscosity). The globule size of the dispersed phase commonly ranges from 0.1 to 100 μm. The pharmaceutical term "emulsion" is mostly used to indicate preparations prepared for internal use.

Do you know?

- Emulsions for external use are always given a different title that it's focus may indicate their use.
- Examples: Lotions, creams, liniments, ointments, vitamin drops, etc.

(b) Classification of Oral Emulsion:

Emulsions are generally classified based on nature of phases in to oil-in-water (o/w), water-in-oil (w/o), and oil-in-oil (o/o). They can also be classified based upon type of dosage form or on structure of the emulsion system.

I. Based on nature of internal and external phase

(i) o/w type emulsion
(ii) w/o type emulsion
(iii) w/o/w or o/w/o emulsion

II. Based on type of dosage form

(i) Lotions
(ii) Liniments
(iii) Creams
(iv) Ointments
(v) Vitamin drops

III. Based on structure of the System:

(i) Macroemulsions: Usual size range 0.1–5 μm; average size 1–2 μm.
(ii) Nanoemulsion: Size range of 20–100 nm.
(iii) Micellar emulsions or microemulsions: Size ranges 5–50 nm.
(iv) Double and multiple emulsions: w/o/w, o/w/o emulsions.
(v) Mixed emulsions: Consisting of two different dispersed droplets that do not mix in a continuous medium, for example, macroemulsions.

(c) Types of Emulsions:

(i) Oil in water (o/w) emulsion: When the oil droplets are dispersed throughout the aqueous phase, the emulsion is termed o/w as shown in Fig. 5.7. Fats or oils for oral administration, either as medicaments, or as vehicles for oil soluble drugs, are always formulated as o/w emulsions. They are non-greasy and are easily removable from the skin surface and they are used externally to provide cooling effect and internally to mask the bitter taste of oil. Water soluble drugs are more quickly released from o/w emulsions.

Remember!

- The o/w emulsion show positive conductivity test as water, the external phase, is a good conductor of electricity.

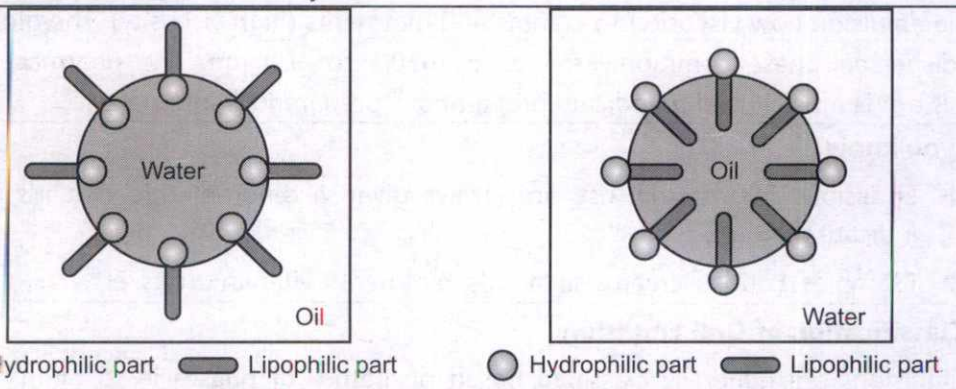


Fig. 5.7: Types of Emulsions: (a) w/o emulsion and (b) o/w emulsion

(ii) Water in oil emulsion: A system in which the water is dispersed as globules in the oil as a continuous phase is termed water-in-oil emulsion. The w/o emulsions have an occlusive effect due to hydration of the stratum corneum and inhibition of evaporation of eccrine secretions. It has an effect on the absorption of drugs from w/o emulsions. Oil soluble drugs are more quickly released from w/o emulsion. They are preferred for formulation meant for external use like cream. A w/o emulsion is not given a positive conductivity tests, because oil is the external phase which is a poor conductor of electricity.

Do you know?

- A w/o emulsion is used to clean the skin consisting of oil soluble dirt.
- The greasy texture of w/o emulsion is not always cosmetically acceptable.
- W/o emulsion is not water washable.
- W/o emulsions prevent evaporation of the moisture from the skin surface.

(iii) Multiple emulsions: Multiple emulsions are complex systems in which the o/w or w/o emulsions are dispersed in another liquid medium. For example, an o/w-in-oil (o/w/o) emulsion consists of very small droplets of oil dispersed in the water globules of a water-in-oil emulsion and a w/o-in-water (w/o/w) emulsion consists of droplets of water dispersed in the oil phase of an oil-in-water emulsion. Multiple emulsions have limitations because of its thermodynamic instability and complex structure.

(iv) Microemulsions: Microemulsion may be defined as dispersion of insoluble liquids in a second liquid that appear clear and homogeneous to the naked eyes. These emulsions are frequently called solubilized systems because on a macroscopic basis, they seem to behave as true solutions. Microemulsions systems consist of water, oil and surfactant, which constitute a single optically isotropic and thermodynamically stable liquid solution. There are three basic types of microemulsions namely; direct, reversed and bi-continuous microemulsions.

Do you know!

- Microemulsion term was first used by Jack H. Shulman, a Professor of Chemistry at Columbia University, in 1959.
- Microemulsions are also termed as, transparent emulsion, swollen micelle, micelles solutions and solubilized oil.

(v) Non-aqueous emulsions: Non-aqueous emulsions are waterless emulsions that produce anhydrous or non-aqueous or oil-in-oil emulsions that may be used as reservoirs to deliver lipophilic or hydrolytically unstable drugs and could be considered as depot formulations for sustained release drug delivery. In these systems, presence of water is avoided. Some drugs are unstable or not soluble in water and formulation of such drug for oral administration is more difficult. These emulsions are used as solvents for drugs, suspension vehicles and oleogels, for example, cyclosporine microemulsion, propofol I.V. microemulsion.

(vi) Liposome emulsions: Liposomes (liposome-lipid based vesicles) are microscopic vesicles, which can be artificially prepared as globular carriers into which active molecules can be encapsulated. Liposome emulsions are those in which o/w emulsions are produced by using liposomes as the emulsifying agent for stabilizing the oil, for example, Lubrizol Liposome Emulsion.

Do you know?

- Liposomes vesicles with diameters between 25 and 5000 nm are used as drug carriers in topical therapeutic preparations for drug delivery, gene therapy, and immunization and in cosmetic products.

(vii) Nanoemulsions: Nanoemulsions are a submicron size colloidal particulate carrier system for drug molecules. Their size varies from 10 to 1,000 nm. These carriers are solid spheres and their surface is amorphous and lipophilic with a negative charge. The term

'nanoemulsion' also refers to a mini emulsion which is fine o/w or w/o dispersion stabilized by very thin interfacial film of surfactant molecule which makes them transparent. They are used to enhance the therapeutic efficacy of the drug and minimize adverse effect and toxic reactions. Nanoemulsions are used in the treatment of infection of the reticuloendothelial system, enzyme replacement therapy in the liver, treatment of cancer, and vaccination.

Remember!

- ❖ Types of nanoemulsion: o/w nanoemulsion, w/o nanoemulsion and bi-continuous nanoemulsion.

(d) Advantages of Emulsions:

(i) Emulsions are non-toxic and non-irritant in nature.

(ii) They can be used in taste masking and to improve physical stability.

(iii) Small-sized droplets provide greater surface area for increased drug absorption.

(iv) They can be formulated as foams, creams, liquids, and sprays.

(v) They help to solubilize lipophilic drugs with less amount of energy.

(vi) They can be used as substitute for liposomes and vesicles.

(e) Disadvantages of Emulsions:

(i) Emulsions are thermodynamically unstable and thus are difficult to manufacture.

(ii) Storage conditions may affect emulsion stability.

(iii) Emulsions are bulky, difficult to transport, and prone to container breakages.

(iv) Liable to microbial contamination which can lead to emulsion cracking.

(v) Emulsions need to be shaken well before use for uniform and accurate dosing.

(vi) Emulsions need a special manufacturing process, instruments, and a trained person.

Methods to Prepare Emulsions...

- ❖ Small scale methods: Dry gum method, Wet gum method and Bottle method.
- ❖ Large scale method: Industrial emulsifiers.

(f) Methods of Emulsion Preparation:

Generally, an o/w emulsion is prepared by dividing the oily phase completely into minute globules surrounding each globule with a layer of emulsifying agent and finally suspends the globules in the aqueous phase. The w/o emulsion is prepared by dividing aqueous phase completely into minute globules, surrounding each globule with a layer of emulsifying agent, and finally suspending them in the oily phase.

(i) Dry gum method: Extemporaneous emulsions are made by continental or dry gum method. The emulsion is prepared by mixing the emulsifying agent (usually acacia) with the oil which is then mixed with the aqueous phase.

(ii) Wet gum method: The proportions of the constituents are same as used in the dry gum method; the only difference is the method of preparation. Here, the mucilage of the emulsifying agent (usually acacia) is formed. The oil is then added to the mucilage drop by drop with continuous trituration.

(iii) Bottle method: This method is a modification of the dry gum method. One part powdered gum is placed in a dry bottle and four parts oil are added. The bottle is capped and thoroughly shaken. To this, the required volume of water is added all at once, and the mixture is shaken thoroughly until the primary emulsion forms.

(iv) In-situ method: In this method no emulsifying agent is used, but it is formed in-situ upon a chemical reaction between the components. This method is effective in preparing an olive oil and lime water emulsion, which is self-emulsifying. Equal parts of lime water and olive oil are added to the bottle and shaken. The oleic acid in olive oil interacts with lime water to form calcium oleate which acts as emulsifying agent.

(v) Membrane method: This method is based on a concept of generating droplets drop by drop to produce emulsion. A pressure is applied direct to the dispersed phase which seeps through a porous membrane into the continuous phase and the droplets formed are then detached from the membrane surface due to the relative shear motion between the continuous phase and membrane surface.

(g) Tests for Identification of Emulsion Type:

Several tests are used for identifying the emulsion type. Although, such tests may be applied rapidly, the results must be interpreted with caution. It may be possible that such tests can not indicate whether a multiple emulsion has been produced? Such controversies may be resolved by microscopic examination (Rawlins, 2005).

(i) Dilution / miscibility test: Miscibility test involves the addition of continuous phase e.g. in case of o/w emulsion; the emulsion remains stable upon unlimited addition of water but will become unstable upon unlimited addition of oil, that is, the oil will separate. Vice versa is the case with w/o emulsion.

(ii) Electrical conductivity test: Water is a good conductor of electricity; hence, an emulsion with water continuous phase will readily conduct electricity while that with oil continuous phase will not.

(iii) Staining test (Dye solubility test): In this test, a small amount of water soluble dye, such as methylene blue is added to the emulsion, now if water is the continuous phase (o/w emulsion), dye will dissolve uniformly throughout the system. If oil is the continuous phase (w/o emulsion), dye will remain as cluster on the surface of the system.

(iv) Cobalt chloride test: When a filter paper soaked in cobalt chloride solution is added to an emulsion and dried, it turns from blue to pink, indicating that the emulsion is o/w type.

(vi) Fluorescence test: If an emulsion on exposure to ultra-violet radiations shows continuous florescence under microscope, then it is Water in Oil (w/o) type and if it shows only spotty fluorescence, then it is Oil in Water (o/w) type emulsion.

(h) Formulation of Emulsion:

Liquid Paraffin Emulsion B.P.

Ingredients	Quantity	Use
Liquid paraffin	50 mL	Laxative
Methyl cellulose 20	2 g	Emulsifying agent
Benzoic acid solution	2 mL	Preservative
Chloroform	0.25 mL	Preservative
Vanillin	50 mg	Flavouring agent
Saccharin sodium	5 mg	Sweetening agent
Purified water q.s. to	100 mL	Dispersion medium

Methods of Preparation:

Mucilage is first prepared by mixing methylcellulose 20 in about six times its weight of boiling water and allowed stand for 30 min to hydrate. An equal weight of ice is added and mechanically stirred to form homogenous mucilage. Vanillin is dissolved in the solution of benzoic acid and chloroform and is added to mucilage and stirred for 5 min. Saccharin sodium solution is prepared in water and added to mucilage. The final volume is made to 10 mL, taking care not to allow air to entrap in the mucilage. The emulsion is prepared by mixing together 10 mL of liquid paraffin and 10 mL of prepared mucilage with constant stirring. It is then passed through a hand homogenizer to make it more stable.

Use: Lubricant laxative for chronic constipation.

(i) Storage of Emulsions:

Emulsions meant for oral use are usually packed in well filled bottles having an air tight closure. Light sensitive products are packed in amber coloured bottles. Viscous emulsions are packaged in wide mouth bottles. Emulsions are stored in a cool place avoiding refrigeration to improve stability. Precautions are taken to prevent microbial contamination.

(j) Quality Control Tests:

(i) Appearance: With visual inspection, the ingredients and the final products are carefully examined for purity and for appearance. The tackiness and texture is observed for extensional and compressional deformation. Odour is determined manually while colour is determined through visual inspection or by colorimeter.

(ii) Identification test: Microscopic examination is a very useful tool to exactly identify type of emulsion produced. The type of emulsion is tested by dilution test, conductivity test, dye solubility test, filter paper test and refractive index test.

(iii) Specific gravity: Specific gravity is a physical constant used to identify emulsion. It is determined by using Pycnometer at a specified temperature.

(iv) pH: The pH of oral emulsion is determined at 25 ± 2 °C, unless otherwise specified in the individual monograph. The pH is determined potentiometrically using pH meter.

(v) Viscosity: Viscosity is determined to assess the changes that might take place during aging. Viscosity can be measured by cup and bob viscometer, cone and plate viscometer or standard capillary tube and rotational viscometer.

(vi) Particle size: Determination of changes in the average particle size is one of the parameters used for assessing emulsion stability. The coalescence rates of emulsion can be assessed by this size analysis using optical microscopy, Coulter counter apparatus, Andresen apparatus or laser diffraction.

(vii) Phase separation: Phase separation rate and its extent after aging of an emulsion may be observed visually or by measuring the volume of the separated phases. It can be examined by degree of phase separation (creaming or coalescence) occurring over a period of time. The test sample is withdrawn from the top and the bottom of the emulsion after specific period of storage and compared the composition of the both the samples by analysis of water content, oil content, or any suitable constituent.

(viii) Zeta potential: Determination of zeta potential is useful for assessing flocculation since electrical charges on particles influence the rate of flocculation. o/w emulsion having a fine particle size exhibits low resistance but if the particle size increases, shows signs of globule aggregation and instability. Zeta potential of an emulsion can be determined by using zeta meter.

(ix) Microbial test: This test is performed to determine preservation efficiency of emulsion. Microbial assay is performed as per method specified under respective monograph.

(x) Assay: This test is performed to determine the presence of active ingredient(s) as mentioned on the label. It is performed by using specified analytical method such as titrimetric or spectrophotometric method or by bioassay.

(xi) Stability testing: The final acceptance of an emulsion depends on stability, appearance, and functionality of the packaged product. Stress conditions employed for evaluating the stability of emulsions that include aging with temperature, centrifugation and agitation.

5.3.5 Suspension

According to BP oral suspensions are oral liquids containing one or more active ingredients suspended in a suitable vehicle. The internal phase of suspension consists of insoluble solid particles of a size 0.5 to 5 μ. The external phase (suspending medium) is generally aqueous in some instance, may be an organic or oily liquid for non-oral use. There are two types of insoluble solids which constitute the internal or dispersed phase.

(a) Definition:

A pharmaceutical suspension is defined as a coarse dispersion in which internal phase consists of insoluble solid particles of a specific size range dispersed uniformly throughout the external aqueous or organic or oily liquid phase with aid of single or combination of suspending agent.

(b) Classification of Oral Suspension:

Pharmaceutical suspensions can be classified based upon route of administration, particle size, therapeutic class, proportion of solids, nature and behaviour of solids and modes of dispensing. Following is the classification of oral suspensions based on therapeutic class and nature and behavior of solids.

(i) Based on therapeutic class:

1. Antacid suspension: Example: Antacid Sucralfate Oral Suspension (Esofate®).
2. Antibacterial suspension: Example: Ciprofloxacin Oral Suspension (Cipro®).
3. Analgesic suspension: Example: Paracetamol Oral Suspension (Panadol®).
4. Anthelmintic suspension: Example: Albendazole Oral suspension (Wintil®).
5. Anticonvulsant suspension: Example: Phenytoin Oral Suspension (Dilantin®).
6. Antifungal suspension: Example: Posaconazole Oral Suspension (Noxafil®).
7. Dry antibiotic powders for oral suspension: Examples: Doxycycline Oral Suspension (Vibramycin®), Azithromycin Oral Suspension (Zithromax®).

(ii) Based on nature and behavior of solids:

1. Flocculated suspension: Cefuroxime Axetil for Oral Suspension.
2. Deflocculated suspension: Paracetamol Oral Suspension Drops (Parald®).

(c) Advantages of Suspensions:

1. Suspension provides better chemical stability to water insoluble drug.
2. Suspension shows sustaining effect as before absorption through dissolution.
3. Suspension can be employed to mask the unpleasant/bitter taste of drugs.
4. Suspensions are more palatable and are easy to swallow.
5. Drugs in suspension exhibit a higher bioavailability because of its large surface area and higher dissolution rate.

(d) Disadvantages of Suspensions:

1. Physical stability, sedimentation and compaction of solids are problematic.
2. Drugs in suspensions are prone to degradation where water acts as a catalyst.
3. Uniform and accurate dosing cannot be achieved unless packed as unit dose.
4. Suspensions are bulky, difficult to transport and prone to container breakages.
5. Preparation requires vigorous shaking before withdrawal from container.

(e) Formulation of Suspension:

Ethambutol Hydrochloride Compounded Oral Suspension U.S.P.

Ingredients	Quantity	Use
Ethambutol Hydrochloride	10 g	Antibiotic
Ora-Plus	50 mL	Suspending vehicle
Ora-Sweet SF q.s. to make	100 mL	Flavouring vehicle

Methods of Preparation:

Accurately weighed ethambutol hydrochloride is comminuting to fine powder. A small quantity of Ora-Plus is added to drug powder and mixed to form a smooth paste. Geometrically, the remainder of the Ora-Plus is added and mixed well. In portions, the Ora-Sweet SF is added and mixed well and then packaged and labelled.

Use: Treatment of pulmonary tuberculosis.

Oral suspensions are prepared by various methods which includes precipitation methods (Organic solvent precipitation, pH change method and precipitation with double decomposition, dispersion methods (Small scale methods such as using mortar and pestle, homogenizer, probe sonication and wet ball milling and large scale method) and extemporaneous methods (from oral solid dosage form and from dry powders and granules for reconstitution).

Do you know?

Physical stability of suspensions is evaluated by...

- ❖ Sedimentation method
- ❖ Rheological method
- ❖ Electrokinetic method
- ❖ Micromeritic method

(f) Storage of Suspensions:

Suspensions are stored in tight containers protected from freezing and excessive heat and light. Unless otherwise specified in monograph liquid oral suspensions are stored in a dry, clean, well ventilated area at room temperature. Suspensions for oral use are packed in wide mouth soda lime or borosilicate glass or plastic bottles with adequate air space above the liquid for proper mixing. Amber coloured glass bottles are used to avoid photodecomposition.

(g) Quality Control Tests of Suspensions:

1. **Visual inspection:** Suspensions are tested for physical instability of powders and granules by noticeable changes in physical appearance, including texture for example, clumping. Discoloration may indicate chemical degradation or microbial contamination of the oral suspension.
2. **pH:** The pH of oral suspension is determined at 25 ± 2 °C using pH meter, unless otherwise specified in the individual monograph.
3. **Assay:** An assay of liquid oral suspension is conducted to determine drug content using suitable analytical method to produce good finished pharmaceutical product.
4. **Uniformity of content:** According to B.P. content uniformity test is applicable for single-dose suspensions. This test is also applicable for oral suspensions that contain drug less than 2 mg or less than 2% of the total mass. According to I.P. unless

otherwise specified, single dose oral suspensions presented in single dose containers that contain less than 10 mg or less than 10 % of drug need to comply this test.

5. **Uniformity of mass:** For this test, the contents of 20 dosage units taken at random are weighed individually, emptied as completely as possible, and the average mass is determined. According to BP this test is applicable for single dose oral suspensions.
6. **Uniformity of volume:** In this test, samples of 10 filled containers are selected and the weight of the contents of each container is determined. The weight per mL is obtained to calculate the net volume of the contents of each container.
7. **Uniformity of weight:** In this test a sample of 10 filled containers is selected and labels are removed. The contents from each container are removed. The containers are dried and again weighed together with its removed parts. The difference between the two weights is the net weight of the contents of the container. According to IP this test is applicable to powders for oral suspensions.
8. **Dose and uniformity of dose:** In this test, using a dropping device the number of drops prescribed for one dose or by means of the measuring device the prescribed quantity is introduced into a suitable graduated cylinder. The dropping speed is 2 drops/sec. The liquid is weighed and addition of drops and weighing is repeated and the process is continued until a total of 10 doses are obtained.
9. **Uniformity of mass of delivered doses:** In this test, 20 doses taken at random from one or more containers along with the measuring device and individually weighed to determine individual and average masses. According to BP this test is applicable for oral suspensions supplied in multi-dose containers.

Other quality control tests used for oral suspensions include consistency, identification, pourability, viscosity, relative density, cap locking, crystallization and precipitation, microbial limit and physical stability testing.

5.3.6 Dry Powder for Reconstitution

Dry powders for reconstitution are marketed as oral reconstitutable medications in unit-dose sachet or multidose bottles. Most drugs prepared as a dry mix for oral suspension are antibiotics. They may contain excipients, in particular, to facilitate dispersion or dissolution and to prevent caking. This dosage form is an alternative form for ready suspensions due to the inherent physical instability and the desired long shelf life.

(a) Definition:

Dry powders for reconstitution are preparations consisting of loose, dry powder mixtures of varying degrees of fine particle size that require the addition of water for reconstitution at the time of dispensing or administration, mostly used for pediatric use.

Objectives of Oral Powders for reconstitution are

- ❖ Improve physical and chemical stability of the drug.
- ❖ Reduce the weight of final product.

(b) Classification of Dry Powder for Reconstitution:

(1) Unit (single) dose powders for oral suspension: A unit dose sachet of powder is administered by sprinkling on the top of a semisolid food, such as jelly or ice cream, or by suspending in a suitable vehicle, such as water or juice, immediately before administration. These are preferred for pediatric and geriatric patients.

(2) Multidose powders for oral suspension: These powders are dispensed in a suitable-sized bottle for reconstitution with water immediately before dispensing.

Dry powder for reconstitution can also be classified as:

(1) Powder blends: Powder blends are mixture of the ingredients in powder form. Ingredients present in small quantities may require mixers for homogeneous dispersion.

(2) Granulated products: Wet granulation is the usual process employed and granulating fluid is usually water but mixture of aqueous/non-aqueous binder solution can also be used.

(3) Combination product: These products contain granules in which majority of the diluent is added after granulation. Heat sensitive ingredients, such as flavours can be added after drying of granules and blended before filling into container.

Examples: Cefuroxime Axetil for Oral Suspension, USP (Ceroxim for Oral Suspension, Sun Pharmaceutical), Cephalexin for Oral Suspension, USP (Ascend Laboratories), Fluconazole for Oral Suspension, USP (Aurobindo), Doxycycline for Oral Suspension, USP (Vibramycin Monohydrate for Oral Suspension, Pfizer), Cefpodoxime Proxetil for Oral Suspension, USP (Rising Cefpodoxime Proxetil for Oral Suspension, Rising Pharmaceuticals, Inc.) etc.

(c) Advantages of Dry Powder for Reconstitution:

1. Use of sachets makes accurate single dosing possible.
2. These preparations have improved appearance and flow characteristics.
3. Packaging in sachets makes the formulation easy to carry.
4. Best suited for pediatric population due to colour, flavour and sweetener.
5. Stable on storage and when reconstituted with an ingestible liquid.
6. Least likely to have chemical stability problems because no heat or solvents are used.

(d) Disadvantages of Dry Powder for Reconstitution:

1. In case of bulk preparation, it may cause dosing accuracy problems.
2. Drug dose upon reconstitution depends on storage temperature, sedimentation rate, viscosity, pourability, redispersion, flocculation and content uniformity.
3. Stability of the reconstituted preparation largely depends on storage temperature.
4. Caking may occur upon longer storage times.
5. There may be loss of the drug during mixing.

Do you know!

- ❖ USP classifies powders as: very coarse powders, coarse powders, moderately coarse powders, fine powders and very fine powders.

(e) Formulation of Dry Powder for Reconstitution:

Gabapentin Oral Powder

Ingredients	Quantity (g)	Use
Gabapentin	0.98	Drug
Xanthan gum	0.20	Suspending agent
Sucrose	2.0	Sweetener
Citric acid	0.03	Buffering agent
Methyl paraben	0.01	Preservative
Amaranth solution	q.s.	Colouring agent
Raspberry flavour	q.s.	Flavouring agent
Purified water for reconstitution	q.s. to 20 mL	Vehicle

Method of Reconstitution:

First type and volume of diluent needed is determined. Gently bottle is shaken to loosen the powder. The cap of the bottle is opened and carefully cool boiled water is added to about half the height of the final marking on the bottle. The cap is replaced and the bottle is shaken until all the powder is thoroughly mixed in vehicle. The suspension is allowed to stand for about 2-5 min to liberate air bubbles in the bottle. Again the cap is opened and carefully water is added to make final volume up to the mark on the bottle. The cap of the bottle is replaced and bottle is inverted and shaken vigorously for at least 5 sec to get an even suspension.

(f) Storage:

The dry powders for reconstitution are packaged in wide mouth container having adequate air space above the powder. For single dosage packing, sachets made up of 4 layers of aluminium foil are used. These dry powders are stored at room temperature in tight container protected from freezing, excessive heat and light. The reconstituted suspension is stored in the refrigerator avoiding freezing or kept at room temperature in a cool dry place below 25 – 30 °C unless otherwise stated.

(g) Quality Control Tests:

(1) Flow properties: Flow properties such as angle of repose, bulk density, tap density and porosity of powder mixture, granulations and combination product should be determined.

(2) Rheology: The rheological behavior of the reconstituted suspensions is determined using Brookfield viscometer (Model – RVT).

(3) pH: The pH of suspensions can be measured using pH paper or pH meter.

(4) Sedimentation:

(a) Redispersability: The redispersability is determined from number of strokes required to redisperse the formed sediment at the end of 7 days of storage of the formulations. (Acceptable when requires NMT 100 strokes).

(b) Sedimentation volume: Sedimentation volume (F) of a suspension is determined as ratio of the equilibrium volume of the sediment (V_u) to the total volume (V_o) of the suspension. The value of F should lie in 0 to 1 range. This value provides a qualitative knowledge about the physical stability of the suspension.

(5) Drug content: The required weight of powder is extracted with 100 mL solvent and the obtained solution is filtered through nylon filter membrane. Accurately 0.1 mL of this solution is further diluted to 10 mL with solvent and absorbance of the solution is measured on UV-spectrophotometer. The drug concentration is extrapolated from the calibration curve in solvent.

(6) *In-vitro* drug release: The *in-vitro* drug release is estimated using USP dissolution test apparatus Type II at 100 rpm. The dissolution medium consisted of 900 mL distilled water maintained at 37±0.5 °C. The drug release at different time intervals is measured using UV spectrophotometer.

(7) Particle size: The average particle size of reconstituted suspension is examined using standard microscope. Average and standard deviations of 100 particles are estimated.

(8) Zeta potential: The reconstituted suspension is diluted with distilled water and zeta potential is measured in triplicates using zeta meter.

(9) Stability: The dry powder is packaged in air tight amber coloured glass bottles and stored for 36 days at 45 °C and then reconstituted with distilled water to make up the volume to 60 mL with gentle shaking. This reconstituted suspension is again stored at 4, 25 and 45 °C for 15 days. These samples stored at various temperatures are evaluated on 7^{th} and 15^{th} day of reconstitution for redispersability, sedimentation volume, drug content, in vitro drug release, particle size and zeta potential.

5.4 TOPICAL PREPARATIONS

Topical preparations are pharmaceutical formulations which contain one or more active ingredients dissolved or uniformly dispersed in a suitable base and any suitable excipients and are normally presented in the form of creams, gels, ointments, or pastes. They are traditionally used for treating topical disorders. The majority of topical preparations are meant for skin applications. Various categories of drugs such as antibacterials, antifungals, antipruritics, local anesthetics, anti-inflammatories, analgesics, keratolytics, astringents and mydriatics are incorporated into these preparations. Drugs incorporated into topical preparations either show their activity on the surface layers of skin tissues or penetrate into internal layers of skin to reach the site of action.

Systemic entry of drugs from these preparations is limited due to various physicochemical properties of dosage forms and biological factors. However, systemic delivery of drugs from topical preparations is feasible by making suitable modifications in the formulation. Topical preparations can also be used in non-therapeutic conditions to provide protective and lubricating functions.

Do you know?

- Topical preparations are used for both local and systemic effects.
- They are designed to deliver drug into the skin in treating dermal disorders, with the skin as the target organ.

5.4.1 Ointments

(a) Definition:

Ointments are defined as homogeneous, semi-solid preparations intended for external application to the skin or mucous membranes that provides emollient, protective, occlusive, therapeutic, or prophylactic functions.

Ointments are formulated using hydrophobic, hydrophilic, or water-emulsifying bases to provide preparations that are immiscible, miscible, or emulsifiable with skin secretions. They can also be derived from hydrocarbon (fatty materials), absorption, water-miscible, or water-soluble bases. Ointments should be smooth and free from grittiness, chemically and physically stable, melt or soften at body temperature and can be easily applied. The base should be non-irritant and should have no therapeutic action. The medicament should be finely divided and uniformly distributed throughout the base.

(b) Classification:

(1) On the basis of penetration:

(a) Epidermic ointments: These ointments are intended to produce their action on the surface of the skin and produce local effect. They are not absorbed into the skin layers. They act as protective, antiseptics and parasiticides.

(b) Endodermic ointments: These ointments are intended to release the medicaments that penetrate into the skin. They are partially absorbed into the skin layers and acts as emollients, stimulants and local irritants.

(c) Diadermic ointments: These ointments are intended to release the medicaments that pass through the skin and produce systemic effects.

(2) On the basis of therapeutic use:

(a) Antibiotic ointments: These ointments are used to kill micro-organisms.

Examples: Bacitracin Ointment, Chlortetracycline Ointment, Neomycin Ointment, etc.

(b) Antifungal ointments: These ointments are used to inhibit or kill fungi.

Examples: Benzoic Acid Ointment, Salicylic Acid Ointment, Nystatin Ointment, etc.

(c) **Anti-inflammatory ointments**: These ointments are used to get relief from inflammatory, allergic and pruritic conditions.

Examples: Betamethasone Valerate Ointment, Fluocinolone Acetonide Ointment, Hydrocortisone Acetate Ointment, Triamcinolone Acetonide Ointment, etc.

(d) **Antipruritic ointments**: These ointments are used to relieve itching.

Examples: Benzocaine Ointment, Coal Tar Ointment, etc.

(e) **Astringent ointments**: These ointments are used to cause skin cells or mucus membranes to shrink, by precipitating proteins from their surface. When applied topically they dry, harden and protect the skin. They reduce bleeding from minor abrasions and are used to relieve skin irritations resulting from minor cuts, allergies, eczema, stretch marks, insect bites and so on.

Examples: Zinc Oxide Ointment, Acetic Acid Ointment, Tannic Acid Ointment, etc.

(f) **Antieczematous ointments**: These ointments are used to prevent oozing and excretion from vesicles on the skin.

Examples: Ichthamol Ointment, Salicylic Acid Ointment, Sulphur Ointment, etc.

(g) **Kertolytic ointments**: These are used to remove or soften the horny layer of skin.

Examples: Resorcinol Ointment, Salicylic Acid Ointment, Sulphur Ointment, etc.

(h) **Counter-irritant ointments**: These ointments are applied locally to irritate the skin, thus reducing or relieving another irritation or deep cited pain.

Examples: Capsicum Ointment, Methyl Salicylate Ointment, Iodine Ointment, etc.

(i) **Antidandruff ointments**: These ointments are used to treat dandruff.

Examples: Salicylic Acid Ointment, Cetrimide Ointment, etc.

(j) **Ointment for psoriasis treatment**: These ointments are used to treat psoriasis.

Examples: Corticosteroid Ointment, Diathranol B Ointment, Salicylic Acid Ointment.

(k) **Parasiticide ointments**: These ointments are used to destroy or inhibit living infestation like ticks and lice.

Examples: Benzyl Benzoate Ointment, Hexachloride Ointment, Sulphur Ointment, etc.

(l) **Protectant ointments**: These ointments are used to protect skin from moisture, air, sunrays or other substances like soap and chemicals.

Examples: Calamine Ointment, Zinc Oxide Ointment, Titanium Dioxide Ointment, etc.

Do you know?

- Non-medicated ointments are used for the physical effects that they provide as protectants, emollients or lubricants.

(c) Advantages of Ointments:

1. Ointments are useful alternatives to avoid first pass metabolism of drug.
2. Ointments are suitable for prolonged site specific application of drug on affected area, avoiding unnecessary non-target exposure of drug and side effects.

3. Handling of ointments is easier than bulky liquid dosage forms.
4. They are chemically more stable than liquid dosage forms.
5. Ointments are suitable for unconscious patients with difficulty in administering drugs by oral and parenteral route.
6. Ointments allow more flexibility in dose.

(d) Disadvantages of Ointments:

1. Ointments have staining properties and are cosmetically less aesthetic.
2. Application with fingertip may contaminate the formulation or cause irritation.
3. Compared to solid dosage forms, ointments are bulky to handle.
4. Using ointments it is difficult to achieve dose accuracy.
5. Ointments are physically less stability than solid dosage forms.

Antimicrobial preservatives used in topical preparations are:

- Methyl paraben, propyl paraben, phenols, benzoic acid, sorbic acid, quaternary ammonium salts.

(e) Formulation of Ointment:

Ointments are prepared either by incorporating the active ingredients into the selected base or by melting the base and active ingredient together. They are prepared by fusion method, trituration method or by chemical reaction method.

Simple Ointment B.P.

Ingredients	Quantity	Use
Wool fat	50 g	Emollient
Hard paraffin	50 g	Stiffening agent
Cetostearyl alcohol	50 g	Emollient
White soft paraffin	850 g	Base

Method of Preparation:

Hard paraffin and cetostearyl alcohol are melted in porcelain dish on water-bath. Wool fat and white soft paraffin are mixed and stirred until all the ingredients melted. If required, decanted or strained and stirred until cold and packed in suitable container.

Uses: Base for white and coloured ointments.

Compound Benzoic Acid Ointment B.P.C. (Whitfield Ointment)

Ingredients	Quantity	Use
Benzoic acid (fine powder)	6 g	Antibacterial agent
Salicylic acid (fine powder)	3 g	Shedding of dead skin cells
Emulsifying Ointment	91 g	Ointment base

Method of preparation:

Benzoic acid and salicylic acid are sieved through No. 180 sieve. These powders are mixed on the ointment slab with small amount of base and levigated until smooth and diluted gradually to obtain final quantity of a formulation.

Use: Treatment of fungal infection of the skin.

Marketed products: Sibex® (Elixir Pharmaceuticals Ltd.), Benzalic® (Central Pharmaceuticals Ltd.), Fungalin® (Chemist Laboratories Ltd.), G-Benzosal® (Gonoshasthaya).

Do you know?

- ❖ USP directs that the labeling for certain ointments and creams include the type of base used (e.g., water-soluble or water-insoluble).

(f) Storage of Ointments:

Ointments dispensed in jars or wide mouth bottles of glass or plastic material are stored at 20-25 °C. They should be stored in tightly closed containers. Sterile ointments are dispensed in tubes or single-dose units in order to protect the product against contamination during use. Ointments are stored to protect from effects of humidity, direct light, heat or cold and out of reach of children and animals.

(g) Quality Control Tests for Ointments:

In addition to physical appearance, identification, particle size, viscosity and assay ointments are tested for:

(1) Weight variation: A total of 10 filled ointment containers are selected, label is removed and outer surface is cleaned, dried and each unit is weighed. If needed container is cut to remove their contents by washing, dried and again weighed along with its parts. Weight variation of the contents is calculated as difference between the weights.

(2) Sterility: This test is applicable to ophthalmic ointments and is performed according to the official monograph by membrane filtration method or direct inoculation method.

(3) Metal particles: This test is applicable for ophthalmic ointments. The ointment from 10 tubes is melted and the contents are collected in Petri dishes. The contents are heated at 85 °C for 2 hours to achieve full fluidity and then allowed to solidify. The Petri dish is inverted on the microscope and bottom of the entire Petri dish is examined for presence of metal particles under 30× magnifications.

(4) *In-vitro* drug release: In-vitro drug release from ointment is tested in Franz diffusion cell using Whatman filter paper (No. 41). Filter paper is soaked in phosphate buffer (pH 6.0) for 24 h at 37±0.5 °C. A thin layer of an ointment is applied to filter paper and the amount of drug permeated is determined using a UV-Spectrophotometer.

(5) **Non-irritancy:** It is performed by patch test daily an ointment is applied on specified area of skin of 24 human volunteers for particular duration and the type of action exhibited is observed. A good ointment shows no visible reaction or erythema or intense erythema with edema and vesicular erosion.

(6) **Rate of penetration:** A weighed quantity of the ointment is applied over specific area of the skin for a definite period of time. The amount of ointment left over on the skin after a specified time is collected and weighed. The difference between weights of the ointment is the amount of ointment penetrated. The rate of penetration is calculated from by dividing amount by area and time period of application.

5.4.2 Creams

Creams are intended for application to the skin or certain mucous membranes for protective, therapeutic, or prophylactic purposes, especially where an occlusive effect is not necessary. The term "cream" is most frequently used to describe soft, cosmetically acceptable types of preparations. As creams are emulsions fatty bases, wax and different oils are used as oil phase and water as aqueous phase. Different emulsifiers are added to form emulsion or there is formation of soap by reaction between fatty acid and alkali during preparation of cream and this soap act as emulsifying agent (in-situ emulsification). The consistency and rheological properties of creams depend on the type of emulsion, either w/o or o/w and on the nature of the solids in the internal phase.

(a) Definition:

Creams are defined as homogeneous, viscous liquid or semi-solid preparations consisting of opaque emulsions of either the oil-in-water (o/w) or water-in-oil (w/o) whose consistency varies with the amounts of oil and water.

(b) Classification of Creams:

1. **Oily creams:** Oily creams are hydrophobic w/o emulsions that are usually anhydrous and absorb only small amounts of water. They contain w/o emulsifying agents such as wool fat, sorbitan esters, and monoglycerides.

   Example: Fluocinolone Acetonide Cream.

2. **Aqueous creams:** Aqueous creams are hydrophilic o/w emulsions that contain water miscible bases. They also contain o/w emulsifying agents such as sodium or triethanolamine soaps, sulfated fatty alcohols, and polysorbates combined, if necessary, with w/o emulsifying agents.

   Examples: Moisturizing Cream, Cold Cream.

3. **Cosmetic creams:** These are both w/o and o/w types of creams used as cosmetic preparations.

   Examples: Cold Cream, Vanishing Cream, Cleansing cream, Foundation Cream, Night and massage Cream, Hand and Body Cream,

4. **Medicated creams:** In this type of cream either w/o or o/w type of cream is used as base so as to carry medicaments.

   Examples: Cetrimide Cream (antiseptic), Zinc oxide Cream (astringent), Hydrocortisone Cream (skin rashes).

Do you know?

- ❖ Cleansing cream is used to remove facial make up, surface grime, oil, etc.
- ❖ It should be soft on application to the skin and spread easily without dragging.

(c) Advantages of Creams:

1. Creams are used to deliver drugs that exhibit a low aqueous solubility.
2. They provide prolong contact at their site of application.
3. Creams help to dry injured area more quickly.
4. Creams are usually non-irritating when applied to the skin.
5. Creams are water washable, less greasy and easy to wipe away.
7. Creams are simple to apply as they spread more easily.

(d) Disadvantages of Creams:

1. Pharmaceutical creams being emulsions are thermodynamically unstable.
2. They are less hydrophobic, so risk of contamination is high.
3. Some of the creams can cause irritation on exposure to sunlight.
4. Application of exact quantity of creams is difficult.

Ideal Characteristics of Creams....

- ❖ It should be non-inflammatory, non-irritant, and non-toxic.
- ❖ Its viscosity should be low enough to permit easy spreading.
- ❖ It should penetrate the epidermis (via natural openings).
- ❖ It should liquefy at body temperature.

(e) Formulation of Creams:

Hydrous Ointment B.P. (Oily Cream)

Ingredients	**Quantity**	**Use**
Wool Alcohol Ointment	500 g	Moisturizer
Phenoxyethanol	10 g	Preservative
Dried magnesium sulphate	5 g	Bulking agent
Purified water (freshly boiled and cooled)	485 g	Vehicle

Method of Preparation:

This cream can be prepared by steps namely; preparation of oil phase, hydration of aqueous phase ingredients, emulsion formation and dispersion of the active ingredients.

The wool alcohol ointment, phenoxyethanol and dried magnesium sulphate are made homogenous using heating and the water is added with constant stirring, followed by mixing vigorously until a smooth cream is obtained and stirring is continued until cold.

Use: Moisturizer in eczema and dermatitis.

Novel Advances in Creams!

- ❖ Albumin microsphere containing vitamin A cream (particle size 222 ± 25 μm).
- ❖ Lamellar faced cream, a liquid paraffin in water emulsion.
- ❖ The o/w cream containing lipid nanoparticles,

(f) Storage of Creams:

Creams are recommended to be stored in dry, well-ventilated area at of 15–25 °C or up to 30 °C. Creams are excluded from extraneous odours, contamination, and intense light.

(g) Quality Control Tests for Creams:

In addition to physical appearance, identification, particle size, viscosity, pH and assay creams are also tested for:

(1) Type of emulsion: The scarlet dye is mixed with the cream and a drop of this mixture is placed on a slide and covered with a cover slip to examine it under a microscope. If the disperse globule appears red and the ground is colourless then it is o/w type and the reverse condition indicates w/o type of emulsion.

(2) Homogeneity: Cream is tested visually for homogeneity in appearance and touch.

(3) Spreadability: Adequate amount of sample is placed between two glass slides and a weight of 100 g is placed on the slides for 5 min. Spreadability is determined from weight applied to upper slide to move glass slide at the length in time.

(4) Removal from skin: The ease of removal of the creams applied to skin is examined by washing the applied part with tap water.

(5) After feel: In this test emolliency, slipperiness and amount of residue left after the application of fixed amount of cream is determined.

(6) Irritancy test: A skin is marked. The cream is applied on the left hand dorsal skin surface area of 1 cm^2 for specified time. It is observed for signs of irritancy, erythema and edema, if any, at regular intervals up to 24 hours.

5.4.3 Pastes

Pastes are the semisolid preparations intended for external application to the skin. Pastes are usually less greasy, more absorptive, and stiffer in consistency than ointments because of the large quantity of powdered ingredients present. Pastes should adhere well to the skin to form a protective film that controls the evaporation of water. Some pastes consist of a single phase, such as hydrated pectin, and others consist of a thick, rigid material that does not flow at body temperature. The bases used for preparation of pastes are hydrocarbon base, water miscible base and water soluble bases. Pastes can also be

prepared by fusion and trituration method. Fusion method is used when the base is semisolid or solid in nature whereas trituration method is used when the base is liquid or semisolid.

(a) Definition:

Pastes are homogeneous, semi-solid preparations containing high concentrations of insoluble powdered substances, usually not less than 20%, dispersed in a suitable base.

(b) Classification of Pastes:

(i) Based on method of preparation

1. Pastes prepared by fusion method. Examples: Zinc Paste, Coal Tar Paste, etc.
2. Pastes prepared by fusion/trituration method. Example: Compound Zinc Paste B.P.

(ii) Based on the type of base

1. **Fatty Paste:** These pastes consist of fatty or oleaginous bases.
   Example: Zinc oxide Paste.
2. **Aqueous gel paste:** These are prepared with water miscible bases.
   Examples: Sodium Hydroxymethyl Cellulose Paste, Titanium Dioxide Paste, etc.
3. **Hydrocolloid paste:** These pastes consist of hydrocarbon bases.
   Examples: Tooth Paste, Zinc Oxide Gelatin Paste, etc.
4. **Medicated Paste:** These pastes consist of medicaments in bases.
   Examples: Potassium Nitrate Medicated Paste.
5. **Non-medicated paste:** These are used as protectants, emollients, or lubricants.
   Examples: Colgate Tooth Paste.

(c) Advantages of Pastes:

1. Pastes easily spread on the skin.
2. Pastes lubricating/emollient properties reduce trauma of an affected site.
3. Pastes persist at the site of application, enabling longer duration of drug release.
4. Pastes protect an inflamed site, for example, in eczema and psoriasis conditions.
6. Pastes may act to absorb moisture and chemicals within the exudates.
7. The opaque nature of pastes enables it to be used as a sunblock.
8. The chemical stability of hydrolytic drugs is enhanced.

(d) Disadvantages of Pastes:

1. Pastes may be greasy and difficult to remove.
2. Pharmaceutical pastes may stain clothes.
3. The viscosity of pastes may be problematic during spreading over the affected site.
4. If drug has limited solubility in the base it may show poor drug release from paste.
5. Pastes have limited applications to the hair due to difficulty in its removal.

(e) Formulation of Paste:

Zinc and Coal tar Paste (White's Tar Paste)

Ingredients	Quantity	Use
Zinc oxide, finely sifted	60 g	Active
Coal tar	60 g	Antiseptic and anti-inflammatory
Emulsifying wax	50 g	Emulsifier
Starch	380 g	Thickening agent
Yellow soft paraffin	450 g	Emollient

Method of preparation:

Emulsifying wax is melted in petri dish at 70 °C. Accurately weighed quantity of coal tar is added to molten wax. Separately yellow soft paraffin is melted and half quantity of molten yellow soft paraffin is added to above molten wax mixture of coal tar with continuous stirring. Remaining quantity of molten yellow soft paraffin is added until it becomes homogeneous. The whole contents are allowed to cool at 30 °C and the zinc oxide (previously passed through sieve no. 180) is added followed by addition of starch with constant stirring. The stirring is continued until paste becomes cold.

Use: For treatment of psoriasis and eczema.

(f) Storage of Pastes:

The pastes are stored in well closed container and in a cool place at a temperature not exceeding 25 °C so as to prevent evaporation of moisture present.

(g) Quality Control Tests for Pastes:

Pharmaceutical pastes are also tested for:

(1) Impurities: Process impurities, synthetic by-products, impurities associated with the adhesive, residual solvents, heavy metals and other inorganic and aromatic impurities entered in pastes are assessed using suitable analytical method.

(2) Water content: A test for water content is performed using Karl Fischer titrator.

(3) Preservative content: The amount of preservative present in multidose pastes is determined using suitable analytical method.

(5) Antioxidant content: The amount of antioxidant present in paste is determined using suitable analytical method.

In addition to above listed tests, other tests include physical appearance, identification, particle size, homogeneity, viscosity, pH, assay and, removal from skin, after feel, irritancy test, and accelerated stability similar to ointments and creams.

5.4.4 Topical Gels

Topical gels are attractive delivery systems being simple to manufacture and suitable for administering drugs through skin, ophthalmic, nasal, otic, and vaginal routes. They provide intimate contact between the drug and the site of action or absorption. Gels respond to

specific biological or external stimuli like pH, temperature, ionic strength, enzymes, antigens, light, magnetic field, ultrasound, and electric current are being designed as smart delivery systems for various applications. Gels are easy to prepare and primarily contain vehicle, gelling agents, buffers, preservatives, antioxidants, flavours/ sweetening agents and colours. Methods of preparation include fusion method, cold method and dispersion method. The principles involved in gelation include thermal changes, flocculation and chemical reaction.

Gels at industrial scale are prepared by ....

- ❖ Thermal changes
- ❖ Flocculation
- ❖ Chemical reaction.

(a) Definition:

Topical gels are defined as homogeneous, clear, semisolid preparations consisting of a liquid phase within a three-dimensional polymeric matrix with physical or sometimes chemical cross-linkage by means of suitable gelling agents meant for topical application.

(b) Classification of Gels:

1. **Hydrophilic gel:** Hydrophilic gel (hydrogel) consists of water, glycerol, or propylene glycol gelled with suitable agents such as tragacanth, starch, cellulose polymers, etc.

   Example: Activegel™.

2. **Non-aqueous gel:** The non-aqueous gel exhibits rheologically physical cross-linked three dimensional gel networks, with suitable mechanical characteristics for use as a vehicle for topical drug delivery.

   Examples: Diclozor® Gel, Hyalu Gel, Hyaluronic Acid Gel.

3. **Organogel:** These are prepared by dissolving/dispersing the organogelator in hot solvent to produce an organic solution/dispersion, which, on cooling sets to the gel.

   Examples: Diltigesic Organogel, Nifedipine and Lidocaine Organogel.

4. **Xerogel:** It is a gel in which vehicle is removed, leaving a polymer network as film.

   Examples: Silica Xerogel, Zinc Oxide/Carbon Xerogel.

5. **Amphiphilic gel:** Amphiphilic gels are prepared by mixing the solid gelator like sorbitan monostearate or sorbitan monopalmitate and the liquid phase like liquid sorbitan esters or polysorbate and heating them at 60 °C to form a clear isotropic sol phase, and cooling the sol phase to form an opaque semisolid at room temperature.

   Example: L-Ascorbic Acid 22% Topical Serum Gel.

6. **Supramolecular gel:** This gel consists of 3-D networks of molecular self-assembly.

   Example: Diclofenac Gel.

7. **Hydrogel:** This gel consists of water and an insoluble hydrophilic polymer. When exposed to water, the dry polymer swells and absorbs liquid to form cross-linked strands either by chemical or by physical forces to immobilize polymer.

   Examples: Hydroheal Gel, Megaheal Gel, Oxalgin Gel.

(c) Advantages of Gels:

1. Gels provide optimal cutaneous and percutaneous drug delivery.
2. Gels are used to avoid gastrointestinal drug absorption difficulties.
3. Gels are used to avoid the first pass metabolism effect.
4. Gels are non-invasive application and have better patient compliance.
5. Gels can be applied over skin for slow and prolonged drug absorption.

(d) Disadvantages of Gels:

1. Gels may be allergic and enzymes in epidermis may degrade drugs in gel.
2. Gels may show poor permeation and bioavailability of large size drugs.
3. Selection of skin area is critical and continued application may cause adverse effects.
4. Gels for application to body cavities, for example, eyes should be sterilized.

(e) Formulation of Gel:

Topical Aceclofenac Gel

Ingredients	Quantity	Use
Aceclofenac	0.375 g	Anti-inflammatory drug
Carbopol 934	0.25 g	Thickening agent
Propylene glycol	2.50 g	Humectant and emollient
Triethanolamine	0.12 g	Buffering agent
Distilled water	21.76 g	Vehicle- Gelling agent

Method of Preparation:

Appropriate quantity of carbopol 934 is soaked in water for a period of 2 hours. Carbopol is neutralized with triethanolamine (TEA) with stirring. Aceclofenac is dissolved in appropriate and pre-weighed amounts of propylene glycol and ethanol. This solvent blend is transferred to carbopol container and agitated for additional 20 min. The dispersion is then allowed to hydrate and swell for 60 min, and pH (6.8-7) is adjusted with TEA. During pH adjustment, the mixture is stirred gently to form homogeneous gel. The dispersion is allowed to equilibrate for at least 24 hours at room temperature.

Use: Anti-inflammatory in arthritis.

Some facts about structure of gels:

- ❖ Gels are formed by gelling agent which is usually a polymer.
- ❖ Gelling agent forms network by interlinking particles to produce rigidity of gel.
- ❖ Type of force and its nature govern the arrangement and properties of gel.
- ❖ The single particles show isometric aggregates or spherical cluster.

(f) Storage of Gels:

Gels are packaged either in large-mouth jars or in metal or plastic collapsible tubes, tight containers, or other well-closed containers. Gels are stored in well-closed containers to protect against contamination and in a cool place to protect against product separation due to heat. Gels are protected from direct sunlight, strong fluorescent light and prolonged exposure to temperatures exceeding 30 °C. When required, light-sensitive gels are packaged in opaque or light-resistant containers. Gels are not to be refrigerated.

(g) Quality Control Tests for Gels:

(1) Alcohol content: Alcohol levels in gels are determined by gas chromatography (GC). The gel sample is dissolved in methanol and injected into a gas chromatograph for quantitative analysis. Isopropyl alcohol or n-propyl alcohol is used as an internal standard and water is used as the diluting solvent.

(2) Rheology: Some of the commonly used tests for characterizing rheology of gels are yield stress, critical strain, and creep. Cup and bob viscometers, cone viscometer, Brookfield viscometer and plate viscometers are used for rheological testing of gels.

(3) Bioadhesion: This test is performed to assess the force of adhesion of a gel with biological membranes. It consists of moving and static platforms. A tissue is fixed onto these platforms. A known quantity of the gel is uniformly applied to the tissue surface of the lower static platform. The upper moving platform is allowed to contact with the gel surface with a known contact force. After a short contact time the moving platform is separated at a constant rate. The force required to detach the tissue surface from the gel is determined.

(4) Stability testing: Syneresis is determined by heating the gels to a higher temperature followed by rapid cooling using an ice water bath at room temperature. The sample is preserved at 4 °C for about a week and water loss from the gel matrix is measured. Absence of syneresis indicates higher physical stability of gels. The chemical stability of drugs in the gel matrix is determined using stability - indicating analytical methods. Accelerated temperature, moisture, and light conditions are used to determine the possible degradation of drug in the gels.

(5) *Ex-vivo* penetrability: Ex-vivo penetrability of gel is determined using vertical diffusion cells or modified cells with flow-through design. The receiver side is filled with phosphate buffer solution (pH 7.4). The stratum corneum layer of skin is

mounted between the donor and receiver sides. Determinations are conducted after application of test gel over the stratum corneum on the donor side. Samples are withdrawn at different time intervals and analyzed for drug permeation.

In addition to tests listed above, other tests include general description, identification, assay, viscosity, homogeneity, pH, removal from skin, after feel, irritancy, etc.

5.4.5 Liniments

Liniments are topical preparations applied with rubbing onto the affected area. Sometimes liniments are called as a heat rub. Liniments have water-like in viscosity and are formulated as a lotion or balm. They are rubbed to allow for penetration of the active ingredients upon melting at body temperature. The oil or soap base provides ease of application and massage. Liniments consist of quickly evaporating solvents such as alcohol, acetone, etc., to increase the penetration effect of aromatic counter irritant such as methyl salicylate, benzoin resin, menthol, or capsaicin molecules through skin. They produce a feeling of warmth within the muscle of the area they are applied to, and act as rubeficients via a counter irritant effect. Liniments are not be applied to broken skin as it can cause skin irritation.

(a) Definition:

Liniments are medicated topical preparations for application to the skin to reduce pain or stiffness from sore muscular aches and strains, or arthritis.

(b) Classification of Liniments:

Liniment may be classified on the basis of therapeutic category, nature of dispersion medium and dispersed phase.

(i) Based on therapeutic category:

(1) Antipruritic liniment: Liniments used to relieve itching. Example: Sanhuang Liniment.

(2) Astringent liniment: Products that causes biological tissue to contract. Example: Kloss Liniment.

(3) Emollient liniment: Products that soften skin or treat dry skin. Example: Bast Liniment.

(4) Rubefacient liniment: These are liniments which causes redness to the skin. **Examples:** Capsicum Liniment, Mustard Liniment, etc.

(5) Analgesic liniment: It is a liniment used for muscle pain or for arthritis pain whose effects can be felt within a few minutes. Examples: Sloan's Liniment, Camphor Liniment, superior analgesic liniment, etc.

(6) Counter irritant liniment: It is a liniment that contains an agent applied locally to produce superficial inflammation to reduce inflammation in deeper adjacent skin. Examples: Methyl Salicylate Liniment, Methyl Salicylate Liniment, etc.

(7) **Anti-inflammatory liniment:** Liniments that reduces inflammation or swelling. **Examples:** Californica liniment, Dhanwantharam Liniment, Kloss Liniment, etc.

(8) **Fungicidal liniment:** Liniments that contain drugs to destroy fungi and inhibit their growth. Examples: Toenail Fungus Liniment, Himalaya Rumalaya Liniment, etc.

(ii) Based on nature of the dispersion medium:

(1) **Oleaginous liniments:** These liniments contain fatty oils (sunflower, linseed, castor oil) or fat-like substance (lanolin) as a dispersion medium. Drugs that can be dispersed include both liquid (chloroform, turpentine, ether, tar) and powder (camphor, menthol, novocaine, dermatol, etc.).

(2) **Alcohol liniments:** These liniments contain alcohol and liqueurs (usually brandy peppers), as well as various medicinal substances.

(3) **Soap-alcohol liniments:** These liniments contain alcoholic solutions of soap as a dispersion medium. They may be liquid if they contain potassium soap or jelly when contain sodium soap and when rubbed on the skin cause emulsification of sebum and rapidly absorbing into the skin, along with drugs.

(iii) Based on type of disperse system:

(1) **Homogenous liniments:** These liniments contained drugs extracted in solvents distributed homogenously in dispersion medium.

(2) **Heterogeneous liniments:** These liniments contained drugs in suspension, emulsion or in combined form, dispersed in medium.

Do you know?

- ❖ Alcohol is the main vehicle used in liniments to increase the penetrating effect of counter-irritant molecules through skin.
- ❖ Liniments are not applied to broken skin as it can cause irritation.

(c) Advantages of Liniments:

1. Liniments are usually non-staining.
2. Liniments are less viscous compared to creams and ointments and gels.
3. Liniments are well absorbed by the skin to exhibit high bioavailability.
3. These are alternative to orally administered dosage forms for drugs.
4. Liniments improve muscle flexibility and provide nerve nourishing properties.

(d) Disadvantages of Liniments:

1. Liniments are meant only for external application.
2. While applying liniments, care needs to be taken to avoid exposure to eyes.
3. Liniments need to be compulsorily stored in coloured fluted bottles.
4. Liniments are not suitable for application on broken skin.
5. To become effective liniments need to be applied with friction by rubbing.

(e) Formulation of Liniment:

Turpentine Liniment

Ingredients	Quantity	Use
Soft Soap	2.7 g	Lubricant
Camphor	1.5 g	Relieve pain, irritation, and itching
Turpentine Oil	19.2 mL	Absorption enhancer
Purified water q.s. to	30 mL	Vehicle

Method of preparation:

Accurately required quantity of soft soap is weighed and dissolved in purified water. The required quantity of camphor and turpentine oil is mixed to form solution. Camphor solution is added to soap solution with trituration until a thick creamy emulsion is formed. The final volume is made by using purified water.

Use: Counter irritant and rubeficients in sore muscles and arthritis.

(f) Storage:

Liniments are packaged in amber glass bottle in an attractive carton. These are stored in a cool and dry place, in an air tight container, away from direct sunlight. Liniments are strictly kept out of reach and sight of children.

(g) Quality Control Tests:

(1) Dilution test: It is performed by mixing 1 mL liniment with 1 mL water. The miscibility of liniment with water is observed. The result of this test determines the type of liniment and the possibility of phase separation.

(2) Stability: Accurately 50 mL liniment is taken in a measuring cylinder and kept aside for 24 hours. After this time, the volume of external phase separated is noted. The phase volume ratio is calculated to establish stability. Phase volume ratio is calculated by equation (6.4):

$$\text{Phase volume ratio} = \frac{\text{Volume of internal phase}}{\text{Volume of linment}} \quad \ldots (5.3)$$

In addition to above tests, other tests such as general description, identification, pH, assay, viscosity, removal from skin, after feel, irritancy etc. may also be performed.

5.4.6 Lotions

Lotions are usually suspension of solids in an aqueous medium. These are light-weight, non-greasy preparations with low-viscosity due to lower water content. Some lotions are, in fact, emulsions, or solutions generally in an aqueous vehicle, although certain solutions have been designated as lotions because of either their appearance or application. Lotions may contain antimicrobial preservatives and other appropriate excipients such as stabilizers. These are intended to be applied to the intact skin without friction.

Do you know?

- Lotions are applied to external skin with bare hands, a brush, a clean cloth, or cotton wool.

(a) Definition:

Lotion is defined as either a liquid or semi-liquid preparation with low-viscosity that contains one or more active ingredients in an appropriate vehicle for topical application to the skin without friction.

(b) Classification of Lotions:

1. **Astringent lotion:** It is a dual purpose lotion that cleanses and moisturizes the face. It helps to remove makeup residue, dirt, dust and other impurities from skin.

   Example: Ayur Astringent Lotion.

2. **Face lotion:** These are called the bleaching lotions, which alters the colour of the skin.

   Example: Oriflame Face Lotion.

3. **Hair lotion:** These are the lotion that has a stimulating effect upon the hair follicles and are generally perfumed with oil of rosemary and other essences.

   Example: Biodens Hair Lotion.

4. **Body lotion:** These are the lotions designed to stop moisture leaving skin, or absorb water from atmosphere to keep the skin soft, smooth and hydrated.

   Example: Olay Body Lotion.

5. **Humectant lotion:** These lotions draw water to the skin cells to keep the skin hydrated.

   Example: Oilatum Lotion.

6. **Emollient lotion:** These lotions fill in any spaces or gaps between skin cells that are missing moisturizing lipids. Emollient lotions, may be oil-based or water-based, makes the skin smoother and better hydrated.

   Example: Parasoft Lotion.

7. **Ceramide lotion:** These lotions replenish the skin with lost ceramides and are better able to retain moisture. Ceramide is naturally found in the skin and damaged or depleted ceramide levels leads to dry and damaged skin.

   Example: Ceramedx Lotion.

8. **Occlusive lotion:** Occlusive lotion contain moisturizing agent(s) that work by forming a protective layer on the surface of skin and creates a barrier to prevent moisture loss.

   Example: Atogla Lotion.

9. **Sunscreen lotion:** Sunscreen lotions absorb or reflect some of the sun's UV rays that protect the skin from its harmful effects such as sunburn, wrinkles and leathery skin.

   Example: Flocare SPF 30 Plus Sunscreen Lotion.

(c) Advantages:

1. Drugs from the lotion are well absorbed by the skin, and have high bioavailability.
2. Lotions may spread thinly to cover a large area of skin.
3. Lotions possess long term stability.
4. Lotions have high water content so viscosity is low.
5. Lotions are non-greasy and suitable for normal or dry skin.
6. Lotions are ideal for day time application and during summer season.

(d) Disadvantages:

1. During application care needs to be exercised to avoid accidental exposure to eyes.
2. Lotions may clog skin pores and increase acne.
3. Lotions can interfere with tretinoin (Retin-A) and alpha hydroxy acids.
4. Lotions may accelerate skin aging and also can irritate skin.
5. Lotions may show systemic side effects such as hyperglycemia and glycosuria.

Do you know?

- Lotions may be spread thinly compared to a cream or ointment and may economically cover a large area of skin.

(e) Formulation of Lotion:

Calamine Lotion I.P.

Ingredients	Quantity	Use
Calamine	9 g	Treat skin irritation and itching
Zinc oxide	3 g	Astringent and antiseptic
Bentonite	1.8 g	Suspending agent
Sodium citrate	0.3 g	Deflocculating and chelating agent
Liquid phenol	0.9 mL	Antiseptic and preservative
Glycerin	3 mL	Humectant
Rose water	60 mL	Aroma

Method of preparation:

Calamine Lotion is prepared by simple solution method with trituration. Sodium citrate solution is prepared by dissolving sodium citrate in $1/4^{th}$ of total volume of rose water. Calamine, zinc oxide and bentonite are triturated with sodium citrate solution until a smooth cream is obtained. The cream is diluted with the water to make it pourable, and this mixture is transferred to a measure. Liquid phenol and glycerin is added to it and mixed well and the final volume is adjusted with the rose water.

Use: Skin protective and soothing for the relief of itching.

(f) Storage:

Lotions are stored in a well closed, narrow mouthed, amber coloured, fluted plastic bottle. Lotions are stored in dry and cool place and protected from exposure to direct sunlight away from sources of heat. They are stored out of reach and sight of children.

(g) Quality Control Tests:

(1) **Spectrophotometric evaluation:** This test determines UV light absorption ability of components incorporated in sunscreen lotion formulation.

(2) **Erythemal dosage:** This test determines the erythemally effective radiation, transmitted by suntan preparations.

(3) ***In-vivo* skin testing:** This is a direct test on animal skin particularly rabbit. The site used for application of lotion is either abdomen or backside of animal as these sites have minimum sensitivity to applied formulation.

In addition to above tests other tests include general description, identification, pH, assay, viscosity, removal from skin, after feel, irritancy etc. are also applicable.

5.4.7 Suppositories

Suppositories are solid dosage forms that for delivery of drugs to systemic circulation or local effects. Suppositories generally consist of drug incorporated into an inert matrix, which is rigid or semi-rigid base. Suppository base is used to disperse or dilute, carry, protect and deliver drug to patient body. Upon administration; suppositories melt due to body temperature and release drug to dissolve in mucosal fluids where drug shows its local effect. The dissolved drug may be transported to systemic circulation to exert systemic effect. Suppositories are prepared in various sizes, shapes, volume and consistency which facilitate their insertion and retention in the body cavities. They are meant for insertion into urethra and nasal cavities, called as 'urethral bougies' and 'nasal bougies', respectively. Suppositories are used to treat constipation and haemorrhoids whereas bougies are used to treat infections of the urethra, prostate, bladder or nose.

(a) Definition:

Suppositories are medicated solid dosage forms intended for insertion into rectum where they melt, soften, or dissolve to exert localized or systemic effects.

Historically...

- Suppositories, pessaries and bougies have been prescribed for the last 2000 years but their popularity as a medicinal form increased from around 1840.

(b) Classification of Suppositories:

1. **Rectal suppositories:** Rectal suppositories are meant for introduction into rectum (anus) for their local and systemic effect. These are tapered at one end; to aid insertion and are frequently wider in the middle before tapering towards the other end; thereby aiding retention in the rectum and enabling the suppository to be

pressed forward by the anal sphincter. They are also cone shaped with rounded apex. Its weight for children is about 1 g and for adults 2 g, torpedoes shape.

Examples: Paracetamol Suppositories I.P. (Antipyretic); GV-SOFT Suppositories (Bliss), Glycerin Suppositories U.S.P. (Laxative); Mesacol® Suppositories (Sun Pharma).

2. **Vaginal suppositories (Pessaries):** These are solid medicated suppositories made for insertion into vagina for local and/or systemic action.

   Examples: Candid CL® (Glenmark), Clotrimazole-200 mg (Glenmark), Clindamycin-100 mg (Sun Pharma Ltd); TODAY® Vaginal Contraceptive (Bliss GVS).

3. **Urethral suppositories (bougies):** Urethral suppositories are meant for insertion into urethra. They are available in long, thin or cylindrical form. Those intended for males weighs 4 g each and are 100-150 mm long while those for females are 2 g each and 60-75 mm in length. These suppositories are very rarely used.

   Example: MUSE® (Alprostadil) Urethral Suppository.

4. **Nasal suppositories (bougies):** Nasal suppositories, also called as 'buginaria', are prepared using glycero-gelatin base and are meant for insertion into nasal cavity. They have similar shape as that of urethral suppositories having weight 1 g and length 1-2 cm.

   Example: Glycerin Suppository.

5. **Ear suppositories:** Ear suppositories, also called as 'aurinaria', are prepared using theobroma oil as a base and are meant for insertion into ear. They are prepared using urethral suppository mould and then cut into required size. Ear suppositories are rarely used.

   Examples: Fleet Glycerin Suppository, Ear Fito-suppository.

(c) Advantages:

1. Suppositories are used to exert local effects on rectal mucosa.
2. These are used to promote evacuation of bowel.
3. They are best alternatives to avoid any gastrointestinal irritation.
4. Suppositories are used for unconscious and post operative patients and for patients with severe nausea or vomiting.
5. They can be used for systemic absorption of drugs and avoid first-pass metabolism.
6. They are suitable for babies or old people who cannot swallow oral medication.

Remember!

- ❖ Suppositories are "bullet" or "torpedo" shaped, pessaries are "bullet" shaped but larger and bougies long and thin, tapering slightly.

(d) Disadvantages:

1. Suppositories suffer from patient acceptability problems.
2. Suppositories are not suitable for patients suffering from diarrhea.

3. The amount of the drug given is either too irritating or is in greater amount.
4. Drug absorption may be incomplete as suppository promotes bowel evacuation.

(e) Formulation of Suppository:

For formulation of suppository drug, suppository base, additives and packaging material are required. Packaging material includes blister, strip and bottle packing as well as plastic disposable moulds.

Glycerin Suppository

Ingredients	**Quantity**	**Use**
Glycerine	91 g	
Sodium Stearate	9 g	
Purified water q.s. to make	105 g	

Method of preparation:

The suppository mould is cleaned and lubricated properly with suitable lubricant. It is kept in inverted position on ice bath to remove excess lubricants from mould cavity. The glycerin is heated with continuous stirring in a porcelain dish on water bath to about 50 °C. Sodium stearate is dissolved with stirring in the hot glycerin and the purified water is added. The excess amount of mixture is immediately poured into the previously heated suppository mold and is placed on ice bath. After cooling to solidification, excess amount is scrapped and the mold is opened to remove suppositories. Suppositories are then wrapped in tin foil or waxed paper and packed into suitable container. While preparing suppository always weight of extra 2 suppositories is taken by considering wastage during transfer of material. For example, to prepare 8 suppositories the amount of drug and base to be taken is for 10 suppositories.

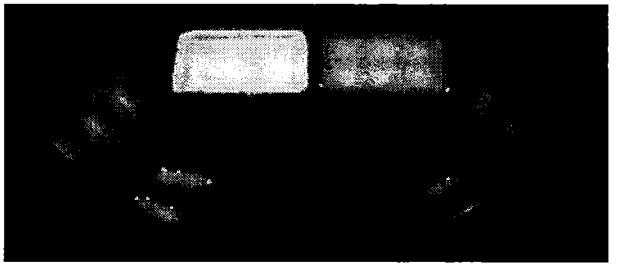


Fig. 5.8: Suppositories and its Mould

(f) Storage of Suppositories:

Suppositories are tightly closed and packed in plastic boxes or in glass containers. Usually suppository must be stored in the original container in a dark and cool environment unless otherwise instructed. Oleaginous suppositories are stored at 30 °C and glycerinated suppositories at 20-25 °C.

(g) Quality Control Tests for of Suppositories:

(1) Water content: Water content in suppository is determined by Karl Fischer titrator using special titration setups and reagents.

(2) Microbial screening: Suitable official microbiological method is used to screen presence of micro-organisms. The plate method or multiple-tube method is performed to estimate the total aerobic microbial counts.

(3) Weight variation: Twenty suppositories are individually weighed and the average weight is calculated. The weight variation is then estimated by subtracting the weight of each suppository from the average weight.

(4) Mechanical strength (Hardness): This test is performed using Erweka hardness tester. The temperature inside the testing chamber is maintained at 25 °C. The suppository is placed into the holding device with the tip upwards and the test chamber is closed. An initial load (600 g) is applied by the entire suspended block and at regular intervals of 1 min a disk of 200 g is added until the suppository crushed. The mass required to crush the suppository is calculated as the sum of the initial load and masses added until the suppository collapsed.

(5) Disintegration test: Disintegration test is performed on six suppositories using tablet disintegration test apparatus. The suppositories are immersed in 160 mL distilled water maintained at 37 °C. The time for complete disintegration of water soluble bases and complete melting of oily bases is determined.

(6) Melting point: The ascending melting point method is used to determine the melting point of suppository. Briefly, capillary tube of 10 cm in length is sealed at one end is filled with the formulation to about 1 cm height. The tube is then dipped in gradually heated electro-thermal thermometer from which the melting temperature of suppositories is determined.

(7) Content uniformity: This test is conducted on 3 randomly selected suppositories by dissolving them in 100 mL phosphate buffer (pH 7.4). Samples of the resulting solutions are appropriately diluted and subjected to absorbance measurement on UV Vis-spectrophotometer at specified wavelength using blank suppository solution. Drug content is calculated using calibration curve equation.

(8) Assay: The quantity of drug present in a unit weight (or volume) of suppositories is determined either by spectrophotometric, titrimetric, chromatographic, or in some cases microbial assays are performed.

(9) *In-vitro* drug release: *In-vitro* drug release is estimated using USP rotating basket dissolution test apparatus in 900 mL Sorensen's phosphate buffer (pH 7.4), similar to tablets.

5.4.8 Pessaries

Pessaries are semisolid form of suppositories and are larger than rectal suppositories. They contain one or more active substances dispersed or dissolved in suitable bases that may be soluble or dispersible in water or may melt at body temperature. Excipients such as diluents, adsorbents, surface-active agents, lubricants, antimicrobial preservatives and colouring matter, authorized by the competent authority, may be added, if necessary. Their weight varies from 4 to 8 g or more hence it requires larger size mould.

Pessary is used in two different ways. In the first sense, a pessary is a pharmaceutical preparation which is used to deliver drugs rapidly through the mucus membranes of vagina to treat vaginal infections. A pessary can also be a supportive device which is inserted into the vagina to treat a variety of medical conditions such as in the management of pelvic support defects and treat stress urinary incontinence.

Pharmaceutical pessaries are available in globular, oviform shaped, rod shaped, wedge shaped or compressed on a tablet press into conical shapes (vaginal tablets) and also available in the form of capsule (vaginal capsule). A pessary is made by blending drugs with a substance which dissolves at body temperature. The drugs will slowly leach through the porous membrane of the vagina. Some medications must be specifically delivered vaginally to be most effective. Pessaries are exclusively used for its local action in vagina except few medications such as prostaglandin, which exert a systemic effect. Commonly used drugs for inclusion into pessaries are antiseptics, contraceptive agents, local anesthetics and drugs to treat trichomonal, bacterial and monilial infections.

(a) Definition:

According to BP pessaries are solid, single-dose preparations with various shapes, usually ovoid, with a volume and consistency suitable for insertion into the vagina.

(b) Method of Preparation:

Nowadays, special shaped suppositories are manufactured and are supplied with applicators to facilitate insertion into the vagina. The pessaries are also available as tablets and capsules and are known as vaginal tablets and capsules, respectively. The pessaries of ichthammol, crystal violet and lactic acid are manufactured by using glycero-gelatin base. Moulded pessaries are packed similar to glycero-gelatin suppositories while tablets containers are suitable for the compressed type pessaries.

(d) Usage:

Pessaries can be inserted using fingers into vagina but for special shaped pessaries, applicators are provided to facilitate insertion into vagina. Sometimes instructions are given on the label to moisten pessaries with water before insertion into vagina to reduce the stinging caused by osmotic withdrawal of the water from the tissues during solution in the vagina, for example, di-iodohydroxyquinoline and nystatin pessaries.

(e) Storage:

Pessaries are stored in a cool place.

5.5 NASAL PREPARATIONS

Drug products applied topically to the mucus membranes of the nose to treat conditions of the nose or nasal symptoms are called nasal preparations. These preparations are formulated as powders, sprays, gels, drops, creams, ointments and solutions for irrigation. They include products such as nasal steroids, lubricants, antihistamines and decongestants and anti-infectives to treat hay fever symptoms, congestion and infections.

Nasal preparations are usually solutions or suspensions administered by drops or as a fine mist from a nasal spray container (aerosol with a metered valve) to treat the nasal symptoms of allergic rhinitis and common cold. A simple drug solution is adequate for this purpose as it produces better dispersion over greater surface area. The nasal residence time of such formulation is about 3-20 min and exhibit high inter-individual variability. This route provides fast peak levels in circulation.

The mechanisms of drug absorption through nasal route involves aqueous route of transport, transport through a lipoidal route and an active transport route via carrier-mediated means or transport through the opening of tight junctions. The factors that affect the systemic bioavailability of nasally administered drugs include physicochemical properties of the drugs, characteristics of other ingredient and type and characteristics of selected nasal drugs delivery system.

Physicochemical properties of drug include its chemical form, polymorphism, molecular weight, particle size, solubility and dissolution rate. Nasal effects such as membrane permeability, environmental pH, mucociliary clearance, cold and rhinitis and delivery effects include formulation parameters (concentration, pH, and osmolarity), drugs distribution and deposition, and formulation effects on mucocilliary clearance and toxic effect on ciliary function and epithelial membranes.

Advantages:

1. Drug degradation is avoided as hepatic first – pass metabolism is bypassed.
2. They show rapid drug absorption and quick onset of action.
3. The bioavailability for smaller drug molecules is good.
4. Nasal preparations are suitable for drugs that are orally unabsorbed.
5. These are alternative to parenterals to deliver protein and peptide drugs.
6. Administration of these drugs by nasal preparations is non-invasive and easy.

Disadvantages:

1. Nasal preparations are primarily suitable only for potent drugs.
2. Drugs for continuous and frequent administration cause harmful long-term effects.
3. Nasal preparations show high variability in the amount of drug absorbed.
4. These are relatively inconvenient to patients due to possibility of nasal irritation.
5. Nasal cavity provides smaller drugs absorption surface through nasal preparations.

Do you know?

- ❖ Nasal congestion is the blockage of the nasal passages because of swollen membrane lining the nose from inflamed blood vessels.
- ❖ Nasal decongestants are vasoconstrictive drugs useful in the common cold.
- ❖ It is used to relieve nasal congestion in the upper respiratory tract.
- ❖ Pseudoephedrine or phenylephrine is the commonly used decongestant.

5.5.1 Nasal Powders

Nasal powders are less frequently used for nasal drug delivery. The suitability of powder formulation is dependent on the solubility, particles size, aerodynamic properties and nasal irritancy of the drug and/or excipients. Spray drying and freeze drying methods are used to produce nasal powders. For a nasal powder formulation, the maximum quantity is approximately 50 mg, depending upon the bulk density of the material. Most of the dry powder nasal preparations are based on mucoadhesive swellable polymers, for example, starch, dextran, chitosan, as they can additionally improve drug bioavailability, prolongs the residence time in the nasal cavity or even promote drug absorption. Powder formulation with water insoluble and non-swellable drug carrier may also improve nasal bioavailability of the polar drugs. Enhanced bioavailability has been primarily ascribed to the retardation of the clearance of the formulation from the nasal cavity. Many small molecules like dihydroergotamine, metoclopramide, butorphanol tartrate, and sumatriptan succinate and larger molecules such as vitamin B_{12}, vasopressin, and calcitonin, have been successfully delivered intranasally in powder form.

Examples: SinuAir Nasal Powder (Health Solutions), Taffix Nasal Powder (Nasus Pharma), Nasowash Powder for Nasal Solution (Cipla), Glucagon Nasal Powder (Eli Lilly and Company).

(a) Definition:

Nasal powders are dosage forms simply formulated by active pharmaceutical ingredients with fillers.

(b) Classification of Nasal Powder Devices:

(1) Insufflators: Insufflations are preparations that are administered using a device called insufflators to deliver the drug substance for inhalation. Insufflator device can be constructed by using a straw or tube which contains the drug substance and sometimes it contains syringe also.

Examples: Progesterone Insufflation, Thalidomide Insufflation, Insulin Insufflation, etc.

(2) Dry powder inhaler (DPI): DPI formulations consist usually of either a drug - only formulation or an ordered mixture of drug and excipient, most commonly lactose monohydrate. The micronization or jet milling methods are employed to achieve drug particle size of 1 – 5 μm. DPIs are devices through which a powder formulation of a drug is delivered for local or systemic effect via the pulmonary route. These are commonly used to

treat respiratory diseases such as asthma, bronchitis, emphysema and chronic obstructive pulmonary disease (COPD) and have also been used in the treatment of diabetes mellitus.

Examples: Albuterol Sulfate Inhalation Powder, Formoterol Dry Powder for Inhalation, etc.

(3) Pressurized metered-dose inhaler (PMDI): A PMDI is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is the most commonly used delivery system for treating asthma, as bronchodilator, COPD and other respiratory diseases.

Examples: Solbutamol Pressurized Inhalation B.P. (Asthalin®; Cipla Ltd.), Beclomethasone Dipropionate and Levosalbutamol Inhaler (Aerocort®; Cipla Ltd.), Ipratropium bromide and Salbutamol (Pulmodual®; Euro-Med Lab).

(c) Advantages:

1. Nasal dry powders an alternative when solution and suspension dosage form cannot be developed, for example, due to lack of drug stability.
2. These are best alternative to parenteral injections and local application of drug is possible as dry powders.
3. Dry powders show prolonged residence time, higher drug concentration at the absorption and enhanced systemic bioavailability.
4. Higher drug concentration at the site of absorption causes rapid transmucosal diffusion and faster onset of action.
5. They are stable formulations with no requirement of preservative and frozen storage or refrigeration.
6. These are simple, easy and safe to reconstitute and are cost-effective.

(d) Disadvantages:

1. Nasal dry powder may cause local tissue irritation of nasal mucosa.
2. Metered dose delivery of nasal dry powders may not be possible.
3. The highest bioavailability of some drugs is markedly decreased upon the repeated administration as nasal powder formulation, for example, insulin.
4. The delivery of drug is not clear from the nasal cavity because of physical barrier.
5. There may be rapid removal of the therapeutic agent from the site of absorption.
6. Pathologic conditions such as cold or allergies may significantly alter nasal bioavailability of drugs.

(e) Formulation of Nasal Powder:

Ketorolac Nasal Powder

Ingredients	Quantity	Use
Ketorolac tromethamine	1.5 g	Anti-inflammatory drug
Microcrystalline cellulose	1.5 g	Absorption enhancer
Water q.s. to	50 mL	Solvent

Method of preparation:

For the dry powder formulation, 1.5 g of ketorolac tromethamine is dissolved in water and added to a hydrated suspension of an equal amount of microcrystalline cellulose. The volume is adjusted to 50 mL, and the contents are lyophilized for 48 h. The formulation is then sieved through 45, 63, and 123 μm mesh sieves and packaged in suitable device.

Positive features of Nasal Powders!

- ❖ Simple composition in excipients (if any).
- ❖ Allow for the administration of larger drug doses.
- ❖ Enhance drug diffusion and absorption across the mucosa.
- ❖ Improved bioavailability compared to nasal liquids.

(f) Storage of Nasal Powders:

Nasal powders are stored at controlled room temperature (20 – 25 °C) and the relative humidity between 40–50% in a sealed packaging. Products may be packaged with secondary packaging in order to protect it from light and/or humidity.

(g) Quality Control Tests for Nasal Powders:

(1) Angle of repose: The angle of repose for powder is measured via the fixed cone height method. Briefly, a glass funnel with an internal stem diameter of 5 mm is placed 1 cm over a glass slide. Particles are allowed to flow gently through the funnel until a cone is formed which has reached the funnel orifice. The angle of repose is estimated from equation:

$$\theta = \tan^{-1}(h/r) \quad \ldots (5.4)$$

Where, h is height of pile and the r is radius of base of the powder pile.

(2) Carr's compressibility index: Carr's compressibility index is an indication of the compressibility of a powder. Carr index is calculated by the formula:

$$C = 100\left(1 - \frac{\text{Freely settled bulk density of the powder}}{\text{Tapped bulk density of the powder}}\right) \quad \ldots (5.5)$$

(3) Emitted dose: The therapeutic effect of aerosols depends upon their drug delivery to the lungs. The first measure of the potential to deliver drug to the lungs is the dose delivered from the device. Two unit dose sampler methods are used to determine emitted dose.

(4) General sizing: Sizing methods include the inertial samplers, cascade impactor and impinger appear. The other methods like thermal imaging can also be used.

(5) *Ex-vivo* nasal perfusion: *Ex-vivo* and *in-vitro* tests are performed to evaluate biological aspects such as permeation, mucoadhesion, cilia and/or cell toxicity, etc. During the perfusion studies, to minimize the loss of drug solution a funnel is placed between the nose and reservoir. The drug solution is placed in a reservoir maintained at 37 °C and is circulated through the nasal cavity of the rat with a

peristaltic pump. The perfusion solution passes out from the nostrils and runs again into the reservoir. The amount of drug absorbed is estimated by measuring the residual drug concentration in the perfusing solution.

(6) ***In-vivo* characterization:** The use of animals to evaluate aerosol performance is conducted by the use of toxicological studies. Instillation and insufflation have been employed to deliver drugs to lungs of various rodent species.

In addition to above test, nasal powders are also tested for general description, identification, particle size, size distribution, melting point and residual moisture, etc.

5.5.2 Nasal Gels

Nasal gels are less viscous and free flowing to allow for repeated administration of drug to the nasal cavity, as droplet mist or as a spray. These are ideal for people using CPAP machines for sleep apnea since the constant flow of air tends to dry out nasal passages. It is very useful in dry climates of low humidity such as indoors during the winter for individuals with nasal allergies or sinusitis. In-situ nasal gels are a liquid formulation when exposed to physiological condition shifts into a gel phase generating a solid or a semisolid depot. Nasal in-situ gels usually have less frequency of applications, long residence time, prolonged drug release, easy to administer and has less systemic side effects.

Example: Entsol Nasal Gel (drug free hypertonic saline gel with aloe and vitamin E).

(a) Definition:

Nasal gels are defined as high-viscosity thickened solutions or suspensions that provide soothing, moisturizing relief to dry, stuffy, irritated nasal passages and used to relieve nasal congestion by reducing edema and swelling, fast and effectively.

❖ An adult nasal cavity has about a 20 ml capacity with a large surface area (about 180 cm^2) for the drug absorption afforded by the microvillus present along the pseudo-stratified columnar epithelia cells of the nasal mucosa.

(b) Classification of Nasal Gels:

(a) Inorganic gels: These are usually two-phase systems. Example: Bentonite magma.

(b) Organic nasal gels: These are usually single-phase systems.

Examples: Carbopol, tragacanth

(c) Nasal hydrogels: Organic hydrogel natural and synthetic gums inorganic hydrogel.

Examples: Methyl cellulose, sodium carboxymethyl cellulose, pluronic, bentonite gel, veegum.

(d) Nasal Organogels: These are hydrocarbon type animal, vegetable, fats soap base greases, hydrophilic organogels, polar, nonionic. Examples: Petrolatum, Mineral oil/Polyethylene gel, Cocoa butter aluminium stearate with heavy mineral oil gel carbowax bases.

(c) Advantages:

1. Nasal gels reduce post-nasal drip due to high viscosity.
2. They reduce taste impact due to reduced swallowing.
3. Nasal gels show less irritation because of presence of soothing/emollient excipients.
4. Nasal gels target to mucosa for better absorption.
5. They offer rapid onset of action as well as bypass first pass metabolism.
6. Nasal gels have increased residence time and show improved patient compliance.
7. They protect the drug from enzymatic degradation.

(d) Disadvantages:

1. Delivery volume in nasal cavity is restricted to 25 – 200 µL.
2. Drug delivery through nasal gel is adversely affected by pathological conditions.
3. Mucociliary clearance and ciliary beating affects the permeability of drug.
4. Some drugs in nasal gel can cause irritation of nasal mucosa.
5. Nasal gels have smaller absorption surface compared with GIT.

(e) Formulation of Nasal Gel:

Venlafaxine Hydrochloride Nasal Gel

Ingredients	Quantity	Use
Venlafaxine Hydrochloride	37.50 mg	Anti-anxiety drug
Carbopol 934	6 %w/v	Absorption enhancer
Sodium alginate	1 %w/v	Mucoadhesion modulator
Nasal solution q.s. to	10 g	Dispersion medium

Method of preparation:

Venlafaxine HCl is dissolved in nasal solution (0.65% NaCl, 0.04% KH_2PO_4, 0.09% K_2HPO_4 and 0.02% benzalkonium chloride) (pH 6) with constant stirring. The required amounts of sodium alginate and Carbopol 934P are added to the solution and stirred on a magnetic stirrer until a uniform solution is obtained which is kept at 4 °C overnight to allow complete swelling so that a homogenous gel is formed.

Use: Treatment of general anxiety disorder.

(f) Storage of Nasal Gels:

Nasal gels are stored in cool and dry place usually in refrigerator. It should not be too cold that gel will 'ice up'. Nasal gels are protected from heat and light as they may get dried up upon exposure.

(g) Quality Control Tests for Nasal Gels:

(1) **Bioadhesion measurement:** A mucoadhesion with mucin is determined by soaking filter paper in a mucin solution to saturate with glycoproteins. The filter is then recovered and the formulation is dropped on it. An air stream (flux = 6.37 m/sec) is applied horizontally onto the filter to simulate the nasal flow and to remove unattached particles.

(2) **Mucoadhesion measurement:** The gel formulation is put into contact with physiological mucus and the viscosity is recorded after a defined period of incubation. Gel samples are analyzed with a plate-plate viscometer. For each viscosity measurement, the value of the control is subtracted to the viscosity measured.

(3) **Formulation tolerance:** This test is done to prove the safety of nasal gels. The test is performed on excised tissue but an alternative method is to deliver the formulation *in-vivo* and recover the tissues after the animal sacrifice. After exposure to the formulation, the mucosa is analyzed by optical microscopy and compared to both negative (phosphate buffer) and positive controls (isopropyl alcohol).

(4) **Isotonicity:** Isotonicity values can be determined from the colligative properties of the solutions. For this purpose, freezing point depression property is most extensively used. The freezing point of water is 0 °C, and when any substance such as NaCl is added to it, the freezing point of water decreases.

(5) **Gelation temperature:** The gelation may be defined as that the temperature at which the liquid phase makes a transition to gel. Gelation temperature can be determined by using modified millers and Donovan technique.

(6) **Gel strength:** The gel strength can be measured by taking 100 g formulation in a 100 mL graduated cylinder and neutralizing it with NaOH solution. A weight of 70 g is placed on to gel. The gel strength is an indication for viscosity of the nasal gel at physiological condition which is determined by time in seconds required for the weight to penetrate 5 cm into the gel. Gel strength can also be evaluated using a Rheometer. The gel containing beaker is raised at a certain rate, pushing a probe slowly through the gel. The changes in the load on the probe are measured as a function of depth of immersion of the probe below the gel surface.

In addition to above tests, other quality control tests include clarity, viscosity, drug content, pH, isotonicity, in vitro drug release, etc.

Do you know?

- In-situ gels are systems applied as solutions or suspensions.
- Undergo rapid sol-to-gel transformation triggered by external stimulus.
- External stimulus may be temperature, pH, ionic strength etc. on instillation.

5.5.3 Nasal Sprays

Nasal sprays are liquid solution or suspension formulations designed to spray directly into the nose, in order to target nasal allergy symptoms without going to the rest of the body. Nasal spray can deliver an exact dose from 25 to 200 µL. The choice of pump and actuator assembly depends upon particle size and morphology of the drug in suspension and the viscosity of the formulation. In a traditional formulation preservative are used but current trend is to develop preservative free formulations. An unpreserved formulation has to rely on the integrity of the primary packaging. OTC nasal sprays contain chemicals such as oxymetazoline, phenylephrine, xylometazoline and naphazoline. A squirt of this nasal spray helps to quickly decongest the nose by constricting the swollen blood vessels in the nasal lining.

Nasal spray devices are used to deliver drugs both locally and systemically, and are readily available as unit dose and metered multi-dose forms. Unit dose devices are used to treat conditions such as migraine pain (Imitrex®), cancer pain (Instanyl®), vitamin B_{12} deficiency (Nascobal®), and heroin overdose (Narcan®); multi-dose devices are for conditions such as allergy (Nasacort®), sinus congestion (Mucinex Sinus®), cold relief (Zicam®), migraine pain (Migranal®), pain management (Sprix®) and nocturia (Noctiva®).

(a) Definition:

Nasal sprays are defined as a liquid medication that is inhaled as a fine spray.

(b) Classification of Nasal Sprays:

There are many types of nasal sprays; both prescription and over-the-counter (OTC).

1. **Nasal steroid sprays:** These are usually one of the first-line therapies for allergies. Nasal steroids work by decreasing inflammation within the nasal passages. These sprays offer relief from nasal congestion, sneezing, watery eyes and runny nose. Many of these sprays are available OTC. Steroids have many side effects (such as cataracts), but these risks are much lower in the nasal form compared to oral form.

   Examples: Generic- Budesonide, Ciclesonide, Fluticasone, etc., and Branded- Rhinocort®, Omnaris®, Zetonna®, Flonase®, Nasonex®, Nasacort®, Xhance®, etc.

2. **Nasal antihistamine sprays:** Nasal antihistamine sprays works similar to oral antihistamines by blocking histamine. These medications are good at treating the runny nose aspect of allergies. The most common reaction is bitter taste.

   Examples: Generic – Azelastine, Olopatadine and Branded – Astelin®, Astepro®.

3. **Combination nasal steroid and antihistamine sprays:** This nasal spray contains both a nasal steroid and antihistamine drug (azelastine and fluticasone). These are currently only available as a prescription product. Example: Branded – Dymista®.

4. **Nasal anticholinergic sprays:** Anticholinergic nasal sprays are good for treating runny nose in patients with both allergic and non-allergic rhinitis. These work by

blocking acetylcholine which decreases secretions from the glands in the nasal passage. Common reactions include dry mouth and bad taste.

Examples: Generic – Ipratropium Bromide and Branded – Atrovent®.

5. **Nasal cromolyn sodium spray:** This nasal spray helps with nasal congestion, sneezing and runny nose in patients with allergies. It works by inhibiting mast cells. It is available as OTC. The most common side-effect is nasal burning and bad taste.

   Examples: Generic – Cromolyn nasal and Branded- Nasalcrom®.

6. **Nasal decongestant sprays:** Nasal decongestant spays provide temporary relief of nasal congestion by constricting the blood vessels in the nose which reduces nasal swelling and congestion. These sprays are good for short periods of time. On using them for more than 3 days they can become addictive to cause a rebound nasal congestion effect called Rhinitis medicamentosa.

   Examples: Generic- Oxymetazoline, Phenylephrine, Xylometazoline, Naphazoline, Neo-Synephrine and Branded- Afrin®, Sinex®, Dristan®, Zicam®.

7. **Nasal saline spray or gel:** These sprays contain saline. The sprays are good to keep the nose moist, and often times these are good for patients who have epistaxis.

   Examples: Generic – nasal saline spray and Branded- Simply Saline®, Xlear®, Ayr®.

8. **Nasal irrigations:** Sterile water that is mixed with salt and often baking soda is flushed into the nose. The idea is to rinse out the mucus out of the nose. These are often used before using a nasal spray. Physician may add steroids or antibiotic ointment to it as well. If used and cleaned properly, these irrigations have less side-effect.

   Examples: Generic – Bulb syringe and Branded - Nettipot®, Neimed®, Ayr®.

Remember!

- ❖ Nasal spray may leave an unpleasant taste in mouth. If this happens, rinse mouth with water.
- ❖ Nasal spray can be used to treat and control chronic rhinitis and allergic rhinitis.
- ❖ It can be used for the relief of nasal congestion due to common colds and flu.
- ❖ Try to avoid sneezing or blowing nose immediately after using the nasal spray.

(c) Advantages:

1. Nasal sprays are non-invasive, painless and easy delivery with favorable tolerability.
2. Drug absorption from nasal spray is rapid.
3. Nasal sprays shows quick onset of action.
4. They are best alternatives to avoid hepatic first – pass metabolism.
5. Using nasal sprays bioavailability of larger drug molecules can be improved.

(d) Disadvantages:

1. Nasal sprays are administered at limited dose due small absorption area available.
2. Bitter taste and time available for drug absorption is limited.
3. Not suitable for diseased nose that may impair drug absorption.
4. Nasal sprays may cause nasal irritation, flushing and headache.
5. Inconsistent absorption and improper use of the spray leads to suboptimal efficacy.

(e) Formulation of Nasal Spray:

Testosterone 1 mg/0.1 mL Nasal Spray

Ingredients	Quantity	Use
Testosterone	1 g	Treats anxiety disorders
Alcohol, 95%	10 mL	Preservative
Propylene glycol	20 mL	Preservative
Benzalkonium chloride	15 mg	Preservative
Purified water q.s. to	100 mL	Vehicle

Method of preparation:

Accurately, each ingredient is weighed. Testosterone is dissolved in alcohol and propylene glycol is added to testosterone solution and mixed well and then benzalkonium chloride solution is added. Slowly sufficient amount of purified water is added to make final volume and mixed well. This preparation is packaged in a calibrated spray container and labeled.

Nasal spray is packaged in non-pressurized dispensers that deliver a spray containing a metered dose of the active ingredient. The dose can be metered by the spray pump. A nasal spray unit can be designed for unit dosing or can discharge up to several hundred metered sprays of formulation containing the drug substance. Energy required for dispersion of the formulation as a spray is accomplished by forcing the formulation through the nasal actuator and its orifice. The formulation and the container closure system (container, closure, pump, and any protective packaging) collectively constitute the drug product.

Use: Bioidentical hormone replacement therapy.

(f) Storage of Nasal Spray:

Nasal sprays bottles are always stored the upright as directed and away from direct sunlight in a clean area. Some nasal sprays are stored at room temperature (20 - 25 °C) while some require use of refrigerator (4 – 8 °C) but not to be freezed.

(g) Quality Control Tests:

(1) Impurities and degradation products: The levels of degradation products and impurities are determined by means of stability indicating method(s). Acceptance criteria should be set for individual and total degradation products and impurities.

All related impurities appearing at levels of 0.1 % or greater should be specified according to ICH guideline for impurities.

(2) **Preservatives and stabilizing excipients assay:** If preservatives, antioxidants, chelating agents, or other stabilizing excipients are used in the formulation, there should be a specific assay for these components with associated acceptance criteria (0.1% or 1 mg/day).

(3) **Particulate matter:** The presence of particulate matter is determined as the cumulative number of particles ≥ 10 µm, ≥ 25 µm, and in some instances ≥ 50 µm.

(4) **Microbial limits:** The microbial quality is tested to determine total aerobic count, total yeast and mold count, and freedom from designated indicator pathogens. Testing should show that formulation does not support microbial growth microbiological quality is maintained throughout the expiration dating period.

(5) **Net content and weight loss:** The total net content of all formulation components in the entire container is determined. The net content of each of 10 test containers is determined in accordance with the release specification.

Other tests include appearance, colour, and clarity, drug content, pH, viscosity, particle size, pump delivery, spray content uniformity, spray pattern and plume geometry, droplet size distribution, priming and repriming, effect of dosing orientation, number of doses and tail-off characteristics and device robustness.

5.5.4 Nasal Drops

Nasal drops are topical aqueous solutions for direct instillation in to nose one drop at a time. These are one of the most simple and convenient systems developed for nasal delivery. Drugs commonly used are anti-inflammatory (corticosteroids, betamethasone), sympathomimetic (ephedrine hydrochloride), decongestants (phenylephrine, oxymetazole, tetrahydrozoline hydrochloride, and oxymetazole hydrochloride), etc. Nasal drops are generally formulated to resemble the nasal secretion and therefore they should be isotonic and slightly buffered, to maintain pH 5.5 – 7.5 using phosphate buffer (pH 6.5). The viscosity of nasal drops should be similar to the viscosity of the nasal secretions and thus is adjusted with the help of thickening agents like methylcellulose; hydroxypropyl methylcellulose. In preparation of nasal drops, generally aqueous vehicles are used. Oils are not preferred as vehicles, because oily drops inhibit the ciliary movement of the nasal mucosa and even causes lipoidal pneumonia (drops of oil enters the lungs). Since the nasal drops is instilled in to nasal cavity, which will be in contact with mucous membrane of nose, it should be clarified by passing through sintered glass funnel before making the final volume with water.

Examples: Ephedrine Hydrochloride Nasal Drops, Phenylephrine Nasal Drops, Oxymetazoline Nasal Drops, Betamethasone Nasal Drops.

Remember!

- ❖ The pH of nasal preparations should be on the acid side to neutral.
- ❖ The buffering capacity of nasal mucosa is high and strong alkaline solution drops containing unbuffered sulphonamides can cause considerable damage to cilia.

(a) Definition:

Nasal drops are aqueous preparations of drugs, intended for instillation into nostrils with the help of a dropper.

(b) Classification of Nasal Drops:

1. **Antibacterial nasal drops:** These are aqueous preparations of antibacterial drugs, intended for instillation into nostrils with the help of a dropper.

   Examples: Oxymetazoline Nasal Drops, Gentamicin Nasal Drops, etc.

2. **Nasal decongestants:** These preparations are used for temporary relief from congestion in the nose caused by various conditions including the common cold, sinusitis, hay fever, and allergies. Nasal decongestants constrict dilated blood vessels within the nose, reducing swelling which allows air to flow more freely, relieving symptoms of congestion.

   Examples: Otrivin® Nasal Drops, Bresol-NS® Nasal Drops, etc.

3. **Nasal antihistamines:** These nasal drops contain antihistamine in a device suitable for nasal use. Nasal antihistamines relieve symptoms such as sneezing, a runny nose, or postnasal drip.

   Examples: Phenylephrine Nasal Drops, Azelastine Nasal Drops, etc.

4. **Nasal lubricants, moisturizers and irrigations:** Nasal lubricants and irrigations are saline solutions or gels used to get rid of a sinus infection. These are used to treat irritated or dry nasal passages caused by hay fever, cold and other conditions. They are also used after nasal surgery to clean out the inner part of the nostrils.

   Examples: Sodium Chloride Nasal Drops, Rhinaris Nozoil Nasal Spray, etc.

5. **Nasal steroids:** Nasal steroids contain corticosteroids such as beclomethasone, budesonide, fluticasone, or triamcinolone in a preparation designed for nasal use. These are effective at reducing inflammation caused by allergies. They relieve nasal and sinus congestion, mucus production, and nasal swelling.

   Examples: Triamcinolone Nasal Drops, Budesonide Nasal Drops, etc.

(c) Advantages:

1. Nasal drops require lower dose and has reduced side effects.
2. They cover large surface area to have rapid absorption, quick onset of action and good bioavailability.
3. These are devoid of gastric drug degradation and hepatic first pass metabolism.
4. Nasal sprays are inexpensive but simple to use by self administration.

(d) Disadvantages:

1. Nasal drops lack in dose precision.
2. These are not used for children as it can cause unconsciousness, convulsions and even death.
3. They may cause regular nose bleeding, rhinitis medicamentosa and sinus dryness and can permanently damage the nasal mucosa.
4. It also can cause irritation, tachyphylaxis, short term stinging, aggravated sinusitis and rebound congestion and headache.

(e) Formulation of Nasal Drop:

Ephedrine Hydrochloride Nasal Drops B.P.C.

Ingredients	Quantity	Use
Ephedrine hydrochloride	0.1 g	Nasal decongestant
Sodium chloride	0.1 g	Tonicity adjustment
Chlorobutanol	0.5%	Preservative
Purified water	20 mL	Vehicle

Method of preparation:

Simple solution method is employed for the preparation of this nasal drops. Chlorbutol, as it dissolves very slowly at room temperature, is vigorously shaken in 3/4th quantity of hot water. During dissolution, conical flask is stoppered to prevent the volatilization of chlorbutol. Upon dissolution the solution is cooled and Ephedrine hydrochloride and sodium chloride are added and dissolved. The solution is then passed through sintered glass funnel or muslin cloth, before making the final volume with water.

Use: Nasal decongestant.

(f) Storage:

Nasal drop are packed in coloured, fluted glass bottle and supplied with dropper. They are stored in a well closed glass container and in cool place. Nasal drops should be used within month after opening the seal of the container. If any unused amount of nasal drops is left, it must be used within a month and discarded after one month.

(g) Quality Control Tests:

(1) Mean delivered dose: The delivered dose measures the amount of medication delivered to the patients and should be close to the target dose as claimed on label.

(2) Delivered dose uniformity: Uniformity of the delivered dose is a critical quality attribute (in-vitro performance) to ensure the quality, efficacy and safety nasal drop.

(3) Content uniformity: The test for content uniformity is based on the assay of the individual content of drug substance(s) in a number of individual dosage units to determine whether the individual content is within the limits set.

(4) **Sterility:** Sterility is an important requirement for nasal formulation. This test is applicable if nasal drops are sterile. The method used is as per pharmacopoeial sterility test.

(5) **Microbial test:** Microbiological quality testing is conducted according to an accepted pharmacopoeial test, or justification is included for not performing this test.

(6) **Preservatives and stabilizing excipients assay:** If formulation contains preservatives, antioxidants, chelating agents or other stabilizing excipients a specific assay for these components is performed to test compliance with associated acceptance criteria.

Other quality control tests include product description, identification, appearance, colour, clarity, viscosity, pH, isotonicity, drug content, formulation tolerance, etc.

5.6 EAR PREPARATIONS

Ear (otic or aural) preparations are products applied to or in the ear to treat conditions of the external and middle ear. These products are used to treat dermatitis of the ear, cerumen build up, ear infection, etc. In general, ear preparations can be ear drops, foams, gels, creams, ointments and powder dosage forms.

Active agents in ear preparations for local use include antibiotics, antifungal agents, anti-inflammatory agents, antiseptics, cleansing solutions and wax softeners. The active ingredients may be dissolved or dispersed in suitable vehicle such as water, diluted alcohol, polypropylene glycol or anhydrous glycerin. These vehicles are inert, non-irritating and viscous that softens the earwax and skin and extend the contact time of the drug with the ear canal surface. The viscosity of ear preparations provides sufficient contact time of dosage form to release the drug at the site of infection effectively. Ear foams are commonly used to increase drug contact time in the ear canal. As volume of dose applied to the ear is low and the concentration of drug in preparation needs to be high. Solubility of the drug is taken into consideration when selecting the proper solvent. Generally, topical ear preparations are prepared in the form of acidic solutions or suspensions with a pH 3-4 for inhibition of bacterial growth.

In the development of ear preparations physicochemical properties such as solubility, viscosity, tonicity, surfactant and preservative properties, serum diffusion activity, impregnation properties, serumolytic activity and rheological properties play an important role. Optimum viscosity for ear preparations provides longer contact time with the ear surface and prevents the leakage of formulation. Low viscosity may cause shorter contact time of formulation while high viscosity may cause lack of reach of the formulation to the inner parts of ear or may be delayed the delivery of drug. The tonicity and hygroscopicity properties are important because they help drawing liquid from the immediate area of the ear. Surfactant helps to spread the drug and break the cerumen and also facilitate removal

of impurities. High concentration of glycerin, propylene glycol, PEG 300 or 400 is used to prevent microbial growth. The commonly used preservatives are 0.5% chlorobutanol, 0.01% thiomersal, and parabens. Other additives include antioxidants, dehumidifying agents and other stabilizers, which reduce the moisture. Ear preparations are usually packaged in small glass or plastic dropper containers with volume of up to 15 mL. Additionally, they can be packaged in puffers, syringes (without needles), or tubes.

(a) Advantages:

1. It exerts direct contact on the organ site and thus is suitable for local effects.
2. It can achieve higher local drug concentration at the site of action.
3. It shows rapid dispersion and has good patient compliance.
4. It has ability to combine different drugs into a single formulation.

(b) Disadvantages:

1. It shows potential ototoxicity of some drugs at high concentrations.
2. Client has to be kept in position for 2-3 min to facilitate drops to reach the site.
3. Accurate dose measurement is not possible.

(c) Types of Ear Preparations:

(i) Ear Drops: Ear drops are solutions, emulsions or suspensions of one or more active ingredient which exert a local effect in the ear. Ear suspensions are used when sustained drug action is desired, or when the drug is not soluble in the vehicles used in ear preparations. These are placed in the ear canal drop-wise for the removal of excessive cerumen (ear wax) or for the treatment of outer ear and ear canal infections, inflammation, or pain. The commonly used vehicles include boiled and cooled purified water and, diluted alcohol, glycerin, propylene or ethylene glycol, etc. Most often non-aqueous vehicles are preferred over aqueous vehicles because aqueous vehicles support and potentiate ear infections. There are four main types of ear drops used to treat ear canal infections (otitis externa):

(i) Antibiotic ear drops: To treat an underlying bacterial infection.

(ii) Corticosteroid ear drops: To reduce swelling.

(iii) Antifungal ear drops: To treat an underlying fungal infection.

(iv) Acidic ear drops: To kill bacteria.

Ear drops are packaged in coloured flutted glass fitted with plastic screw cap with glass dropper or squeezing plastic bottles with suitable dropper. The volume of ear drop preparation packaged in a container is usually maximum 15 mL. The label indicates "For external use only", "Not for injection" and "Discontinue use if irritation persist". Usual dose to be instilled in each ear is 3-4 drops.

Examples: Floxin® Otic, Ciprodex® (Novartis), Debrox® Ear Drying Drops, etc.

Sodium Bicarbonate Ear Drops

Ingredients	Quantity
Sodium bicarbonate	7.0 g
Phenol	0.5 g
Glycerin	50 mL
Purified water q.s to	100 mL

Method of Preparation: Sodium bicarbonate is dissolved in previously boiled and cooled 40 mL purified water. Separately calculated amount of phenol is dissolved in glycerine. This mixture is gently warmed to dissolve glycerine by applying heat below 50 °C. Both these solutions are mixed and transferred to measuring device and make up the final volume. The complete process is performed aseptically.

Use: To soften dry and hardened earwax.

(ii) Ear Irrigating Solutions: Ear Irrigating solutions are used for irrigating the ear to remove earwax buildup. Otic irrigating solutions may consist of surfactants, weak sodium bicarbonate, boric acid (0.5 - 1%), or aluminum acetate solutions. These solutions may be warmed to 37 °C before instillation into the ear. Irrigating solutions may also be used to remove purulent discharges of infection and foreign bodies from the ear canal.

Examples: Boric acid 2-4%, Sodium bicarbonate solution 1%, Normal saline, Hydrogen peroxide 2% and plain warm water.

(iii) Ear Ointments and Gels: Ear ointments and gels are semisolid preparations that are applied to the exterior of the ear. Any ointment base can be used in their preparation of antibacterial, antifungal, or corticosteroid ear ointments.

Examples: Otomax® Otic Ointment for Animals (Merck), Tritop® Otic Ointment for Dogs and Cats (Zoetis), Tech-Care Ear-Gel (Harris Communications), Osurnia® Otic gel for dogs.

(iv) Ear Insufflations: Ear insufflation is an innovative therapy where small puffs of powder/air are applied to the ear drum to relieve the patient from migraines, headaches, sinus issues, and more. Insufflations are preparations made of finely divided powders that are administered to the ear canal. Insufflating a powder into the ear canal is not common because the ear lacks fluids and a powder-wax buildup may occur. Fine powders used as insufflations may contain antibacterial and/or antifungal drugs that create a repository for the drug. A small rubber or plastic bulb insufflator (powder blower, puffer) can be used to blow, or insufflate, the powder into the ear.

Examples: CSF Otic Insufflation (Edge Pharma),

Otic Powder and Capsules

Ingredients	Quantity
Chloramphenicol	46.7%
Sulfamethoxazole	46.7%
Amphotericin	5.6%

CSF Otic Powder is a simple, effective method for dry-powder treatment of ear. Powder adheres to moist surfaces and has a longer dwelling time than liquid preparations. The preparation contains chloramphenicol and sulfamethoxazole, and the antifungal amphotericin B.

Use: To treat chronic otitis media and otitis externa.

(d) Storage:

Ear preparations are stored at either room or refrigerated temperatures and are not to be frozen. The important directions on these preparations include "For the Ear", "Discard after Appropriate Date", "Use Only as directed" and "Keep out of Reach of Children".

(e) Quality Control Testing:

Quality control tests for ear preparations are performed according to standard quality control procedures such as identification appearance, odour and assay, volume/weight, pH, viscosity, density, etc.

5.7 POWDERS AND GRANULES

Solid dosage forms such as tablets, capsules, granules, sachets, powders and granules, etc., are important dosage forms in pharmaceuticals. These dosage forms contain unit dose of one or more medicament along with excipients such as binders, glidants, sweeteners, etc. The solid dosage forms are the most commonly used dosage form because of the easy handling, good stability and ease of mass production. Powder as a dosage form enhances therapeutic activity or efficacy of drugs by an increase of dissolution rate and/or absorption. Divided powders are convenient for administering drugs that are excessively bitter, nauseous, or otherwise offensive to the taste. Powdered drugs can be blended with other powdered materials (additives) prior to fabrication into other solid dosage forms.

A good powder formulation has a uniform particle size distribution. A non-uniform particle size distribution may result in inaccurate dosing or inconsistent performance. A uniform particle size distribution ensures a uniform dissolution rate, a uniform sedimentation rate and minimizes stratification. Uniform particle size can be achieved by particle size reduction (comminution). The particle size can be reduced by trituration, pulverization by intervention or by levigation.

(a) Definition:

A pharmaceutical powder is defined as a solid dosage form which contains mixture of finely divided drug(s) and excipients in a dry form meant for internal or external use.

(b) Classification of Powders:

Powders for pharmaceutical use can be classified as follows:

1. Powders for internal use

(a) Divided powders

(i) Simple powders

(ii) Compound powders

(iii) Powders enclosed in cachet

(iv) Tablet triturates

(b) Bulk powders

(i) Antacid powders

(ii) Laxative powders

2. Powders for external use

(a) Dusting powders

(i) Medicated dusting powders

(ii) Surgical dusting powders

(iii) Cosmetic dusting powders

(b) Powders for insufflation

(c) Douche powder

(d) Powder Dentifrices

3. Special powders

(a) Eutectic mixtures

(b) Effervescent powders

Do you know?

- Medicated powders may be bulk powders or divided powders.
- Bulk powders are non-toxic and can be measured a spoon.
- Divided powders are properly blended powders which are divided into individual dosing units for a single time use.

(c) Advantages of Powders:

1. Drugs in large doses are best administered in powder form by mixing them fluids.
2. Powders are more stable and convenient to swallow.
3. Powders dissolve rapidly in the GIT fluid that minimizes local irritation.
4. Rapid dissolution of powder facilitates rapid absorption.
5. Manufacturing of powder is simple and economic; hence product cost is quite low.

(d) Disadvantages of Powders:

1. Potent drugs cannot be administered in large doses.
2. Powders are inconvenient to carry and often unstable at normal storage conditions.
3. Powders are not suitable for drugs inactivated in, or cause damage to, stomach.
4. Powders are not suitable for oral administration of bitter and nauseating drugs.
5. The masking of unpleasant tastes may be a problematic with powders.

5.7.1 Insufflations

Insufflation is the practice of inhaling a substance. It is defined as the act of blowing a powder, vapor, or gas into any body cavity for experimental, diagnostic, or therapeutic purposes. Insufflation preparations can be medicated dusting powders meant for introduction into the body cavities such as nose, throat, ears and vagina with the help of an apparatus called insufflator. The depression of device's rubber bulb causes turbulence of the powder in the vessel, forcing it out through the orifice at the tip and sprays the fine powder as a stream over the site of application. Thus, insufflations are in finely divided powders so that a stream of fine particles of drugs could be applied to the site of application. Sometimes insufflations may be used for the nose, for example, Pituitary Insufflation B.P.C., absorbed by nasal mucosa when sprayed into the nose, similar to the snuffs. Normally lactose is used as diluent in insufflation for wounds and maize starch for rough skin surfaces.

Specialized equipment used for the administration of micronized powders of relatively potent drugs, for example, Norisodrine Sulfate Aerohaler Cartridge (Abbott). Inhalation using Aerohaler by the patient causes a small ball to strike a cartridge containing the drug. The force of the ball shakes the proper amount of the powder free, permitting its inhalation. Another device, the Spinhaler Turbo-inhaler (Fisons), is a propeller-driven device designed to deposit a mixture of lactose and micronized cromolyn sodium into the lung as an aid in the management of bronchial asthma.

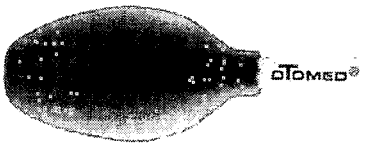


Fig. 5.9: Sheehy-House Powder Insufflator (Source: www.gracemedical.com)

Nasal insufflation is commonly used for many psychoactive drugs because it causes a much faster onset of action. Some drugs have a higher rate of absorption, and are thus more effective in smaller doses, through this route. Insufflations are also used to produce a local effect, for example, treatment of ear, nose and throat infection with antibiotics or to produce a systemic effect from a drug that is destroyed in the gut.

The major limitations of insufflators are difficulty in obtaining uniform dose due to clumping of particles that it gets blocked when it is slightly wet or the powder used is moist. Thus, insufflations must be stored in dry place. Currently, the insufflations are available in the form of pressurized devices like aerosols. Aerosol form has the advantage of excellent control of dose through metered valves. In addition, it protects the product from external environment.

Do you know?

- Snuffs are finely divided solid dosage forms of medicaments dispensed in flat metal boxes with hinged lid.
- Powders as snuff are inhaled into nostrils for decongestion, antiseptic, and bronchodilator action.
- Hygroscopic powders absorb atmospheric moisture but remain in solid state.
- Deliquescent powders absorb moisture and become liquid.

(a) Advantages:

1. Rapid, safe, non-invasive and convenient method.
2. Suitable for potent drugs as limited volume can be sprayed into the nasal cavity.
3. Avoids drug degradation in the gastrointestinal (GI) tract.
4. Avoids first-pass metabolism allowing enhanced bioavailability.
5. Reduction of systemic side effects.
6. Rapid drug absorption via highly vascularized mucosa and faster onset of action.
7. Ease of administration.

(b) Disadvantages:

1. Rapid elimination of drug from nasal cavity due to mucociliary clearance.
2. Nasal congestion may interfere with this technique of drug delivery.
3. Frequent use may lead to mucosal damage and/or irritation of nasal mucosa.
4. Drug loss could occur due to improper administration.
5. They need to be finely divided powder form to generate a stream of fine particles.

(d) Uses:

Drugs administered through nasal insufflation have a local effect or a systemic effect and has the potential capacity to result in increased onset times. The examples of drugs given as insufflation includes steroids (for local effects) and anti-asthma medication, hormone replacement, decongestants (for local effects), nicotine replacement, migraine medication, vaccines, etc.

5.7.2 Dusting Powders

Dusting powder (or medicated dusting powder) is a powder preparation consisting of a powder or a mixture of several powders used for the skin or on wounds for therapeutic, hygienic, or cosmetic purposes. These powders are applied in very fine form (passed through sieve no. 85 (180 μm) to enhance effectiveness and avoid local irritation. The excipients used in dusting powders are powdery, chemically inert plant substances such as various starches, and mineral substances such as talc, zinc oxide, kaolin. The basic criteria for selection of dusting powders are use of natural excipients, talc-free, smooth and silky finish post application, a mild, unique fragrance, absorb moisture effectively and come in an easy to carry containers.

By drying and cooling the skin, dusting powder relieves inflammation. Its hygroscopic particles adsorb perspiration and sebum and increase the surface of evaporation and heat exchange. Dusting powders are used to treat acute skin inflammations, to cleanse the skin when there is increased sweating or seborrhea, to protect the skin from external irritations (solar rays), and to make ointments and creams adhere better to the skin.

(a) Classification of Dusting Powders:

(1) Medicated dusting powders: Medicated dusting powders are used for superficial skin conditions. These dusting powders are mainly used for their antiseptic, astringent, absorbent, antiperspirant, and antipruritic action. The dusting powders are non-toxic but its inhalation by infants may cause pulmonary inflammation and thus utmost care needs to be exercised while handling dusting powder for use in infants.

Medicated Dusting Powder

Ingredients	Quantity
Talc	51 g
Kaolin	15 g
Precipitated chalk	21 g
Zinc stearate	3 g
Boric acid	5 g
Salicylic acid	5 g
Perfume	q.s.

Sterilized talc is a major ingredient in medicated dusting powder formulation, which should have good slip characteristics, covering power and body adhesion. Currently, corn starch, arrowroot starch, rice starch, tapioca starch, kaolin clay, oats flour have replaced the harmful talc. In order to improve adhesion properties, zinc stearate or magnesium stearate and kaolin are incorporated. To improve absorbency, magnesium carbonate, starch, kaolin and precipitated chalk are used in combination. Zinc oxide and titanium dioxide, at low levels along with earth colours can be incorporated to cover the base odour. Other ingredients included are boric acid to act as skin buffering agent and fused silica to give powder a lower density; salicylic acid for antibacterial action. Aluminum chloride is also incorporated as an antiperspirant.

(2) Surgical dusting powders:

Surgical dusting powders are intended to be used into deep layer of skin, in body cavities, burn wounds and umbilical cords of patients. Surgical dusting powders must be sterilized to make it free from pathogenic microorganism before their use.

Neosporin Dusting Powder

Ingredients	Quantity
Bacitracin	5000 IU
Neomycin	3400 IU
Polymyxin B	400 IU

Bacitracin topical is used alone or in combination with neomycin and polymyxin to treat and prevent superficial and minor skin infections due to wounds, cuts or burns. Bacitracin

acts by inhibiting the growth of bacteria in the wounds thereby relieving associated symptoms. Neomycin prevents the bacterial growth by stopping the production of essential protein in the bacterial cells, thereby relieving the associated symptoms. Polymyxin B works by killing the bacteria that causes the infection.

(3) Cosmetic dusting powders:

Cosmetic dusting powders contain various oils, special dyes, fragrances, and essential oils. These powders are prepared by mixing different powders such as kaolin, talc and starch.

The following is an example of dusting powder prepared from good quality natural powder ingredients.

Cosmetic Dusting Powder

Ingrdients	**Quantity**
Kaolin clay	1 part
Arrowroot powder	2 parts
Essential oil(s)	q.s.

Method of Preparation:

1. Mix 1 part kaolin clay to 2 parts arrowroot powder.
2. Add essential oils, for example, rose geranium and lavender. The essential oils will form droplets, simply stir them into the powder and their fragrance will diffuse throughout.
3. Use spoon or a funnel to fill containers. Extra powder can be stored in a sealed glass jar or sealed bag.
4. Wear a mask to cover nose and mouth while preparing this powder mixture.

Kaolin clay is a fine, soft natural absorbent powder that help to prevent chafing and rashes. Arrowroot powder is a fantastic base in its fine form as it absorbs extra moisture. Essential oil(s) provides fragrance to dusting powder to freshen up in a summer when it becomes sweaty. Adding natural scents such as oils of lavender, vanilla, rose, etc., to these dusting powders create a cooling and calming sensation.

(b) Advantages of Dusting Powders:

1. Dusting powders are useful when excess perspiration/exudates need absorption.
2. Dusting powders can be employed as lubricants, protective, absorbents, etc.
3. These powders have good chemical stability compared.
4. These powders are easy to carry and apply over wounds with rapid onset of action.
5. Dusting powders economical and suitable for children and elderly patients.

(c) Disadvantages of Dusting Powders:

1. These powders are not intended for systemic action and not applied to broken skin.

2. Dusting powders containing hygroscopic ingredients are prone to hydrolysis.
3. Not suitable for drugs unstable in normal storage condition.
4. These powders are susceptible to physical instability.

(d) Packaging, Application and Storage of Dusting Powders:

Dusting powders are dispensed in large glass; metal or plastic containers fitted with a perforated lid. The powders are applied with powder puff or sterilized gauze pad. These powders are stored in tightly closed containers, protected from heat, light and moisture.

5.7.3 Effervescent Powders

Effervescent powders are mixtures of powdered materials which react in presence of water to evolve carbon dioxide. These powders preparations are dispensed in the form of salts or supplied either in the form of granules. The constituents responsible for evolution of the gas are a soluble carbonate, for example, sodium bicarbonate and an organic acid, for example, citric or tartaric acid. The effervescent powders can be supplied either as a bulk powder or distributed in individual powders. The methods of preparing effervescent powders are as follows:

1. If the effervescent salt is to be prepared in divided doses, the ingredients responsible for effervescence upon mixing with water are packed separately in papers of different colour. The patient is directed to take one powder of each colour and add to water, before use. The quantities of the sodium bicarbonate and the organic acid (citric or tartaric) are equimolecular in proportion.
2. The ingredients are mixed uniformly and directions stated on the label to add the prescribed quantity to water, before use.

Example: Paramax® Effervescent Powder

Paracetamol	500 mg
Metoclopramide hydrochloride	5 mg

Other ingredients used in Paramax® Effervescent Powder include sodium carbonate, saccharin sodium, lemon flavour, sodium dihydrogen citrate (anhydrous), sodium bicarbonate and gelatin.

Paramax® is a combination effervescent powder product containing paracetamol and metoclopramide. Paracetamol is a analgesic (painkiller) drug. It helps to relieve the pain that a patient feel during a migraine headache. Metoclopramide hydrochloride is an anti-sickness drug, also called anti-emetics. It works on muscles in the upper part of the digestive system causing stomach to empty. It also works on a part of brain that prevents from feeling sick (nausea) or being sick (vomiting). It does this in part by moving the food in patients stomach through his/her digestive system more quickly. Paramax® is used to treat the signs of migraine, such as headache, nausea or vomiting, in adults. Paramax® is not given to patients under 18 years of age.

Limitations of effervescent formulations:

1. It cannot be given to the children because of possibility of gas (CO_2) toxicity.
2. Improper packaging leads to degradation by environmental moisture.
3. It has shorter shelf life as compared to other solid dosage forms.
4. It requires special machinery requirements for manufacturing.
5. This dosage form is costly then tablets.

5.7.4 Effervescent Granules

(a) Granules:

Granules are large agglomerates of small fine or coarse particles prepared by granulation techniques. Generally, granulation begins after initial dry mixing of the powder ingredients along with the drug(s), so that a uniform distribution of each ingredient throughout the powder mixture is achieved. Granules are generally having particle size in the range of 0.2-4.0 mm. They are produced to attain the uniformity of the drug content in the final product, to increase the density of the blend so that it occupies less volume per unit weight, for better storage and shipment, to facilitate metering or volumetric dispensing, to reduce dust during granulation process to reduce toxic exposure and process-related hazards, and to improve the appearance of the product.

The ideal properties of granules include spherical shape for improved flow, narrow particle size distribution for content uniformity and volumetric dispensing. The properties of the particles acquired after granulation depends upon the particle size of the drug and excipients, the type, concentration, and volume of binder and/or solvents, granulation time, type of granulator, drying rate (temperature and time), etc. The methods involved in granule formation include solid bridges, sintering, chemical reaction, crystallization and deposition of colloidal particles. In addition, binding can also be employed through adhesive and cohesive forces using highly viscous binders. The mechanisms involved in granules formation include wetting and nucleation, coalescence or growth, consolidation, and attrition or breakage. The granulation technique used to facilitate the agglomeration of powder particles are dry granulation and wet granulation. Granulation technologies like roller compaction, spray drying, supercritical fluid, low/high shear mixing, fluid bed granulation, extrusion/ spheronization, etc., have been successfully used.

(i) Advantages of Granules:

1. Granules are easy to handle because of its better flowability.
2. These are suitable for high dose stable drugs with weak compressibility.
3. Dissolution rates of hydrophobic drugs can be improved by granulation.
4. Granules reduce air entrapment dustiness and segregation.
5. Granules maintain good content uniformity as they have the same density.
6. Granules are more stable against humidity and atmosphere.

(ii) Disadvantages of Granules:

1. Granules are expensive because of its multistep and complex manufacturing.
2. Loss of material takes place during various stages of granulation.
3. Not suitable for thermolabile drugs and may have incompatibility problems.
4. Not suitable for administering potent drug with low dose.

(b) Effervescent granules:

Effervescent granules are uncoated granules containing acid substances and carbonates or hydrogen carbonates which react rapidly in the presence of water to release carbon dioxide. They are specially prepared for internal use. They contain a medicament mixed with citric acid, tartaric acid and sodium bicarbonate. Sometime saccharin or sucrose may be added as a sweetening agent. Before administration, the desired quantity is dissolved in water; the acid and bicarbonate react together producing effervescence. The carbonated water produced from the release of carbon dioxide serves to mask the bitter and saline taste of drugs. Additionally, carbon dioxide stimulates the flow of gastric juice and helps in the absorption of medicament. Effervescent granules are prepared by heat method and wet method.

Things to Remember!

- ❖ Effervescent granules are preferred over small powder particles to decrease the rate of solution and to prevent violent and uncontrollable effervescence.
- ❖ Sudden and rapid effervescence could overflow the glass and leave little residual carbonation in the solution.
- ❖ Effervescent granules are prepared by dry or fusion method and wet method.

(i) Dry or Fusion method: In this method, the one molecule of water present in each molecule of citric acid acts as the binding agent for the powder mixture. The sieves and the mixing equipment should be made of stainless steel or other material resistant to the effect of the acids. The mixing of the powders is performed as rapidly as possible in a low humidity environment to avoid absorption of moisture and a premature chemical reaction. Before mixing the powders, the citric acid crystals are powdered and then mixed with the other powders of the same sieve size to ensure uniformity of the mixture. After mixing, the powder is placed in dish maintained at 34 °C to 40 °C. During the heating process, an acid resistant spatula is used to turn the powder. The heat releases the water of crystallization from the citric acid, which, in turn, dissolves a portion of the powder mixture, setting the chemical reaction and consequently releasing some carbon dioxide. This causes the softened mass of powder to become somewhat spongy. When it has reached the proper consistency, it is removed from the oven and passed through a sieve to produce granules of desired size.

(ii) Wet Method: The wet method uses water as source of binding agent. The mixed ingredients are moistened alcohol to prepare a coherent mass. The water is added to alcohol as the moistening agent, which forms the pliable mass for granulation. In this method, all of the powders may be anhydrous as long as water is added to the alcohol. The liquid is added in portions to prepare a mass of proper consistency. This mass is then passed

through a No. 8 sieve to obtain granules which are dried in an oven at a temperature not exceeding 60 °C. The dried granules are again passed through the sieve to break the lumps which may be formed during drying. The dried granules are then packed in air tight containers or sealed package and stored in dry place to prevent premature effervescent.

Examples: Urisol® Effervescent Granules (Sodium Bicarbonate + Tartaric Acid + Sodium Citrate Anhydrous + Citric Acid Anhydrous), Urivin® Effervescent Granules (Piperazine citrate + Colchicine + Khellin + Atropine sulphate + Citric acid anhydrous + Sodium bicarbonate).

(c) Advantages Effervescent Granules:

(1) Rapid onset of action and rapid disintegration and dissolution.

(2) Liberated CO_2 act as local anesthetic to mask the undesirable drug taste.

(3) It exerts psychological effect which make patient feel comfortable to it.

(4) It provides alkaline solution upon neutralization of acidic drugs.

(d) Disadvantages Effervescent Granules:

(1) Effervescent granules become unstable upon absorption moisture from atmosphere.

(2) In case of effervescent granules estimation of accurate dose is difficult.

(3) Due to sodium overload these granules are not suitable for hypertensive patients.

(4) Effervescent granules may have drug-drug interactions.

Quality Control Tests for Powders and Granules:

(1) Abrasiveness: This test is applicable to powders. It is determined by rubbing the powder on a surface and then studying the effect on the surface using microscope.

(2) Bulk and tapped densities: This test is applicable to powders and granules. It is significant for estimation of bulk volume, flow characteristics and compressibility. The powder is passed through a no. 18 sieve into a pre-weighed 25 mL graduated cylinder with 0.5 mL markings. The bulk volume is measured after tapping the cylinder two times on a flat table top surface. The tapped volume is measured with the tap density tester after tapping in increments of 500, 750, and 1250 taps with 250 drops per minute.

$$\text{Bulk density} = \frac{\text{Bulk mess}}{\text{Bulk volume}} \quad \ldots (5.6)$$

$$\text{Tapped density} = \frac{\text{Mass of granules}}{\text{Volume of granules}} \quad \ldots (5.7)$$

(3) Hausner ratio: This test applicable to powders and granules. It is indicative of flow properties. It is derived property from bulk and tapped density. Lower the Hausner ratio is indicating better flow whereas higher ratio indicates poor flow of granules. Hausner ratio is calculated by the following formula:

$$\text{Hausner ratio} = -\frac{\text{Tap density}}{\text{Bulk density}} \quad \ldots (5.8)$$

(4) Moisture content: This test applicable to powders and granules. Percentage of moisture content determined by loss in weight and is calculated by using formula:

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad \ldots (5.9)$$

(5) Antimicrobial activity: This test applicable to dusting powders. The antimicrobial activity of dusting powder is tested by well-diffusion using cup plate method against *Staphylococcus aureus* and *Escherichia coli.*

Other quality control tests include physical characteristics, particle size, angle repose, Carr's compressibility index, pH etc.

5.8 STERILE FORMULATIONS

Sterile formulations are type of dosage forms free from any microorganisms, dust, fibres, and foreign particles, and should be isotonic with the body fluids. Injectable dosage forms are sterile formulations injected directly into body tissue through the skin, and mucous membranes. Injectables must be exceptionally pure and free from physical, chemical, and biological contaminants. These formulations are called parenterals. The word parentral is derived from the Greek words para (outside) and enteron (intestine). Injectables are usually supplied in single dose glass or plastic containers or in pre-filled syringes or pens to facilitate the ease of use. Parentral preparations may also be prepared for multiple administrations.

Eye (or ophthalmic) preparations are sterile liquid, semi-solid, or solid preparations that contain one or more drugs and are intended for application to the conjunctiva, the conjunctival sac, or the eyelids. The most common ophthalmic dosage forms are solutions, suspensions and ointments. These dosage forms accounts for nearly 90% of currently available ophthalmic formulations in the global pharma market. The individual shares are 62.4% (solutions), 17.4% (ointments), and 8.7% (suspensions). Sterility is a most important parameter in manufacture and use of ophthalmic products.

Sterile formulations are administered in the form of injection or directly to the eye because certain active ingredients such as peptides, proteins, and chemotherapeutic agents get inactivated in the GIT if taken orally and thus administration by ophthalmic route.

Do you know?

Sterile formulations should be....

- ❖ Pyrogen free
- ❖ Isotonic
- ❖ Free from the foreign particles.

5.8.1 Injectables

Parenteral preparations are defined as sterile and pyrogen free solutions, suspensions, emulsions of drug in aqueous or oily vehicles for injection or infusion, powders for injection or infusion, gels for injection and implants meant for introduction into the body by means of an injection under or through one or more layers of the skin or mucous membrane.

(a) Classification of Injectables:

1. **Liquid solution for injection:** Liquid injectables are sterile preparations of drug substances or solutions thereof. They may be made with aqueous or oily vehicles.

   Examples: B Complex Injection, ProZinc Injection, Meloxicam Injection, etc.

   Oily injectables are used for introduction into the body by means of an injection under or through one or more layers of the skin or mucous membrane.

   Examples: Dimercaprol injection, Oily Phenol Injection, Salvarsal Oily Injection, etc.

2. **Powder for injection:** It is a powder intended for injection following reconstitution in suitable solvent to form a solution or suspension.

   Example: Cefuroxime for Injection, Sodium Aescinate for Injection, etc.

3. **Colloidal solution for injection**: A colloid is a high molecular weight substance that mostly remains confined to the intravascular compartment and thus generates oncotic pressure.

   Examples: Natural colloids: Albumin, fresh frozen plasma, etc.

   Artificial colloids: Gelatin, dextran, hydroxyethyl starch, iron, etc.

4. **Injectable emulsion:** These are liquid preparations of drug substances dissolved or dispersed in a suitable emulsion medium.

   Examples: Propofol Emulsion Injection, Vitamin A, D and E Emulsion Injection, etc.

5. **Injectable suspension:** These are liquid preparations of solids suspended in a suitable liquid medium.

   Example: Amoxicillin Suspension for Injection, Methylprednisolone Acetate Suspension for Injection, Desoxycorticosterone Pivalate Suspension for Injection, etc.

6. **Infusion fluid**: This is a liquid preparation containing medication, nutrient, or other fluid given by parentral route, usually over minutes or hours, either by gravity flow or often by infusion pumping.

   Examples: Normal (isotonic) Saline.

   Parentral preparations may also be categorized as following:

   (1) Based on types of packaging or dosing:

   (a) Single dose units: Ampoules, infusions and prefilled disposable syringes.

   (b) Multiple dose units: Multiple dose vials.

   (2) Based on the production and control:

   (a) Small volume parenterals: Volume <100 mL

   Examples: Furosemide Injection, Heparin Injection, Cimetidine Injection, etc.

   (b) Large volume parenterals: Volume ≥ 100 mL

   Examples: Infusion Fluids, Total Parenteral Nutrition Solutions, Dialysis Fluids.

(3) Based on clinical use:

(a) Solutions for irrigation

(b) Ophthalmic solution

(c) Dialysis solution

(d) Diagnostic agent

(e) Allergenic extracts

(f) Implants

(4) Based on physical state of product:

(a) Sterile solutions

(b) Sterile suspensions

(c) Sterile emulsions

(d) Sterile solids

(5) Based on route of administration:

(a) Intravenous injection: Drug is directly administered into the blood veins.

(b) Intramuscular injection: Drug is directly administered into large skeletal muscles.

(c) Intra-peritoneal injection: Drug is administered into the peritoneal cavity.

(d) Subcutaneous: Drug is injected just below the skin.

(e) Intra-dermal injection: Drug is given into the skin so it forms a small bulge.

(f) Intrathecal: Here drug is administered into the spinal cord.

(g) Epidural: The drug is injected near the spinal cord to affect the local nerves.

(h) Intraosseous: The injection is directly administered into the bone marrow.

Sterile formulations are administered by...

- ❖ Injection
- ❖ Infusion
- ❖ Implantation

(b) Advantages of Injectables:

1. Injectables are reliable and precise in dosage and show rapid onset of action.
2. Injectables are best in emergency conditions, for example, in heart failure.
3. They have ability to provide control over drug delivery to the administrator.
4. Avoids first pass metabolism of drugs which are destroyed in liver.
5. Drugs can be administered at low drug concentration with minimum wastage.
6. They have low toxicity as compared to solid dosage form.

7. Suitable for drugs which are degraded or unreliably absorbed orally.
8. Parenterals are best when patient is unconscious and cannot swallow the medicine.

(c) Limitations of Injectables:

1. Injectable drugs are expensive as compared to solid dosage form.
2. Injectables are highly risky if any mistake happens during administration.
3. Through injectables distribution cannot be stopped once administered.
4. For injectables needs to be sterilized else can lead to microbial growth.
5. Injectables require trained personnel for its administration.
6. Injectables have chances of pain and injury at site of injection.

(d) Essential Requirements of Injectables:

1. All injectable products must be sterile.
2. All injectable products must be free from pyrogens (endotoxins).
3. Injectable solutions must be free from visible particulate matter.
4. Injectable products should be isotonic.
5. All injectable products must be chemically, physically and microbiologically stable.
6. Injectables must be compatible with i.v diluents, delivery systems, and other drug products co-administered.

Do you know?

- ❖ Inert gases are used to avoid chemical degradation in the products.
- ❖ Nitrogen is the most commonly used inert gas

(e) Formulation of Injectables:

(1) Small volume parentrals (SVP):

The volume of SVP is less than 100 mL. The large-scale production of SVP requires appropriate adjustments in the processes and their control. A master formula is developed and each batch formula is prepared from the master formula. All quantities of materials are measured accurately and checked by qualified responsible person. Care needs to be taken that equipment is not wet enough to dilute the product significantly or, in the case of anhydrous products, to cause a physical incompatibility. The sequence of mixing of excipients may affect the product significantly. Many of active ingredients are usually extremely sensitive to temperature, mixing time and speed, order of addition of excipients, pH adjustment and control, and contact time with various surfaces like filters and tubing. The assurance of attaining product stability requires a high order of pharmaceutical knowledge and responsibility.

Examples: Enoxaparin Sodium Injection I.P., Ascorbic Acid Injection I.P., Amikacin Sulphate Injection, etc.

Ascorbic Acid Injection I.P.

Ascorbic acid	25 g
Sodium bicarbonate	14.58 g
p-chloro m-cresol	0.1 g
Water for Injection I.P.	100 mL

Method of Preparation:

This injection is prepared in aseptic room under a laminar airflow hood in a clean room using strict aseptic technique. Ascorbic acid solution is prepared by transferring 2/3rd of the total volume of water in a beaker. Ascorbic acid is weighed and suspended in water with continuous stirring. Sodium bicarbonate is slowly added with vigorous stirring to produce effervescence. After subsidizing the effervescence, remaining sodium bicarbonate is added. This process is continued till ascorbic acid completely dissolves. Then p-chloro m-cresol is added and stirred to dissolve. The pH is adjusted to 5.7 and the solution is filtered through G-4 filter. The 2 mL ascorbic acid solution is aseptically transferred to ampoules and heat sealed.

Use: Vitamin C deficiency.

Do you know?

- **Small Volume Parenterals...**
  - ❖ Supplied in single or multiple doses.
  - ❖ The volume is generally less than or equal to 100 mL.
  - ❖ They are used to dispense most of the drugs.
- **Large Volume Parenterals...**
  - ❖ Delivered through I.V. route.
  - ❖ Supplied for single dose having more than 100 mL.

These generally provide electrolytes, nutrition to the body.

(2) Large volume parentrals (LVP):

LVPs are single-dose injections having a volume of 100 mL or greater that are intended for I.V. use and are packaged in containers labeled as containing more than 100 mL. LVP products administered by I.V. routes are called as transfusion fluids or intravenous infusions. They are sterile aqueous solutions or emulsions with water for injections as the main component. They also incorporate other ingredients including carbohydrates such as dextrose, sucrose, dextran, etc., amino acids and lipid emulsions which contain vegetable or semisynthetic oils, electrolytes such as sodium chloride and polyols such as glycerol, sorbitol and mannitol. Manufacturing of SVP involves additional step of sequential mixing of ingredients to attain homogeneity which requires considerable mixing time. The most common sizes of LVP are 100, 250, 500, and 1,000 mL. Generally, they are packaged in plastic bags due to its less weight, more compact storage, and disposable. They may be packaged in glass bottle for drugs that interact with plastic bags such as nitroglycerin and amiodarone.

Examples: Sodium Chloride Solution, Dextrose Solution, Ringers Solution, etc.

Normal Saline Solution:

Sodium chloride I.P.	0.9 %
Sterile Water for Injection I.P.	200 mL

Method of Preparation:

The Normal Saline Solution for injection is prepared in aseptic room under a laminar airflow hood using strict aseptic technique. Accurately weighed sodium chloride is dissolved in 95 mL of Sterile Water for Injection. Once dissolved sufficient Sterile Water for Injection is added to make the final volume and mixed well. The mixture is filtered through a sterile 0.22 µm filter into a sterile appropriate container, packaged and labeled.

Use: Nutritional supplement.

(3) Lyophilized products:

Lyophilized (or freeze dried) products are solid dosage form prepared by freeze drying (lyophilization) process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor (sublimation) without passing through a liquid phase. The process consists of three separate, unique, and interdependent processes namely freezing, primary drying, and secondary drying. The products obtained by freeze drying can also be called as dry injectables. Dry injectable product is packaged as dry solids because therapeutic agent is unstable in the presence of liquid component; usually a water. These dry powders are packaged in the final container to be reconstituted, generally to a solution or less frequently a suspension. The common examples of drugs processed by lyophilization are antibiotics, anticancer drugs, enzymes and biological components such as cells, tissues and membranes. In addition, there are many new parenteral products, including anti-infective, biotechnology derived products, and *in-vitro* diagnostics which are manufactured as lyophilized products. These lyophilized products have problems associated with the manufacture and control of potency, sterility and stability.

Examples: Doxorubicin Hydrochloride Lyophilized Powder for Injection I.P., Cephalothin Lyophilized Powder for Injection, Dobutamine Lyophilized Powder for Injection, etc.

Doxorubicin Hydrochloride Injection I.P.

Doxorubicin hydrochloride	50 mg
Lactose monohydrate	250 mg
Water for Injection I.P.	2 mL

Method of Preparation:

The formulation is prepared in aseptic room under a laminar airflow hood in a clean room using strict aseptic technique. Accurately doxorubicin hydrochloride and lactose monohydrate are weighed and dissolved in about 3.5 mL of Sterile Water for Injection. Sufficient amount of Sterile Water for Injection is added to make up final volume and mixed well. The solution is lyophilized in freeze dryer by prefreezing, primary drying and secondary drying and finally vacuum sealed.

Use: Anticancer

(f) Storage of Injectables:

Proper environmental control must be maintained while storing injectables. Usually liquid injectables are stored between 25 °C to 30 °C. An emulsion injectable should be stored at cool place in air tight container, protected from light and freezing. Injectable suspension should be stored in a cool place but not be kept in a refrigerator. Freezing of suspension injectables at a very low temperature should be avoided as it may lead to aggregation of the suspended particles. Lyophilized injectables are stored at 4-8 °C, protected from heat and light.

Production facilities for sterile formulation include...

- ❖ Preparation area
- ❖ Aseptic area
- ❖ Finishing and packing area
- ❖ Quarantine area
- ❖ Clean Up area

(g) Quality Control Tests for Injectables:

1. **Identity tests:** These tests, for example, colour formation, precipitation etc., are qualitative chemical methods used to confirm the actual presence of compound.
2. **Quality tests:** These tests, for example, absorbance, refractive index, etc., are the physical methods used to measure accurately the characteristic properties of drug.
3. **Purity tests:** Purity tests, for example, tests for clarity of solutions, acidity, alkalinity, etc., are performed to estimate the level of all known and significant impurities and contaminants in the drug substance under evaluation.
4. **Potency tests:** Potency tests are assays that estimate the quantity of an active ingredient in the drug product.
5. **Sterility test:** Sterility test determines complete absence of all forms of micro-organisms in injectables. The methods used to perform sterility testing are direct transfer method and membrane filtration method.
6. **Test for pyrogen:** Pyrogens are metabolic products of micro-organisms. Pyrogens are produced by gram negative bacteria. These are heat stable, lipopolysaccharides which are capable of passing through bacteria retentive filters. They produce a mark response of fever with body ache and vasoconstriction when injected into the body within an onset of 1 h. The presence of pyrogen is tested by Sham test and Rabbit test. Sham test is a preliminary test used to detect presence of pyrogens in parenteral products.
7. **Bacterial endotoxin test:** The Lysates of Amebocytes of Limulus (LAL) test is used to detect the presence and concentration of bacterial endotoxins in injectables. This test utilizes gelling property of Lysates of Amebocytes of Limulus Polyphemus derived from horse shoe crab.

8. **Leaker test:** Leakage test is performed to test the package integrity such as capillary pores or tiny cracks that are present on the vials or ampoules. This test is conducted by placing ampoules in a vacuum chamber and completely submerging in 0.5 to 1% methylene blue solution. A negative pressure is applied making the dye to penetrate through any opening, if present, on the ampoule. The container is then inspected for the presence of dye either visually or by means of UV spectroscopy.
9. **Particulate matter test:** The procedure employed in this test for LVP's involves filtration followed by microscopical examination. For SVP's a light obscuration based sensor containing electronic liquid borne particle counter system is used.
10. **Clarity Test:** Clarity test involves the visual assessment of formulation in light on suitable background. The transparent particles are observed against the black background and the black or dark particles observed against a black and white background.
11. **Content uniformity and weight:** This test determines the content of the active ingredient in each of 10 containers selected at random. The preparation under examination must comply with the test if the individual values obtained are all between 85 and 115 % of the average value.
12. **Extractable volume test:** This test is used to determine total volume of contents filled in a container. Each container of an injection is filled with sufficient excess of the labeled volume. Individually contents of each container selected are withdrawn into a dry hypodermic syringe. The contents of the syringe are discharged, into a dry graduated cylinder. The volume (mL) is calculated as the weight (g) of injection taken divided by its density.
13. **Stability testing:** Stability testing is performed to provide evidence on how the quality of an active substance or pharmaceutical product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. This helps to determine identity, strength, quality and purity throughout the shelf life of products.

Other quality control tests used for injectable products include pH, viscosity, isotonicity, osmolality, conductivity, etc.

Do you know?

- **Small Volume Parenterals...**
  - ❖ Supplied in single or multiple doses.
  - ❖ The volume is generally less than or equal to 100 mL.
  - ❖ They are used to dispense most of the drugs.
- **Large Volume Parenterals...**
  - ❖ Delivered through i.v. route.
  - ❖ Supplied for single dose having more than 100 mL.
  - ❖ These generally provide electrolytes, nutrition to the body.

5.8.2 Eye Drops

Eye drops are preparations used to treat a wide range of eye conditions such as an infection, an allergy, a minor eye injury, to relieve dry or red eyes, for post-operative healing or in chronic conditions like glaucoma. These drops are the most convenient, safe, immediately active, patient compliant and non-invasive dosage forms. An eye drop solution provides pulse drug permeation upon instillation, after which its concentration rapidly declines. Therefore, to improve drug contact time, permeation and ocular bioavailability; various additives may be added to topical eye drops such as viscosity enhancers, permeation enhancers and cyclodextrins.

The choice of any excipients used for the preparation of eye drops must not affect adversely either the stability of the final product or the availability of the active ingredients at the site of action. Eye drops supplied as multidose preparations may include a suitable antimicrobial agent. Single-dose containers for surgical use should not include any antimicrobial agents.

(a) Classification of Eye Drops:

(1) Eye drop solutions:

Eye drops are saline-containing drops used as an ocular route to administer. Solution eye drops are sterile, aqueous solutions used for, among other things, cleansing and rinsing eyeballs. They may contain excipients, which, for example, regulate osmotic pressure, the pH, and viscosity of the preparation. They may also contain preservatives if stored in multiuse packaging. Solution eye drops sometimes do not have medications in them and are only lubricating and tear-replacing solutions. Eye drop are isotonic, preservative free, solutions with a near neutral pH of 6.8.

Examples: Osmodrops Eye Drop, Ciprofloxacin Eye Drop, Moxifloxacin Eye Drop, etc.

Moxifloxacin Hydrochloride Ophthalmic Solution 0.5%

Moxifloxacin	5 mg/mL
Boric acid	10.2 mg/mL
Purified water	5 mL

Method of Preparation:

The manufacture of eye drops usually involves the dispersion of the sterile drugs into the sterile vehicle with added excipients and subsequent packaging, both under aseptic conditions. Production under clean conditions is followed by sterilization by autoclaving (moist-heat sterilization) or by filtration. As eye drops must be sterile, usually an aseptic manufacturing process is employed. Typically eye drop solutions may be manufactured and packaged in the final container under clean conditions. Clarification of the solution is performed by filtration through 1 μm filter under aseptic conditions. Packaging must be adequate to protect these preparations from light, moisture, microbial contamination, and damage due to handling and transportation.

Use: Anti-infective for the treatment of bacterial conjunctivitis, for treatment of keratitis and as a prophylaxis agent in cataract and refractive surgeries.

(2) Eye drop microemulsions:

Eye drops in emulsion form offers to improve both solubility and bioavailability of drugs. These drops are generally dispersions of oily droplets in an aqueous phase. As some of the lipid-soluble drugs has problems in formulating them as aqueous solutions in such cases microemulsion are a valid alternative. The examples of drugs that can be formulated as eye drop emulsions include difluprednate, azithromycin, cyclosporine, flurbiprofen axetil, etc. The o/w emulsion is common preferred due to less irritation and better ocular tolerance. Eye drop emulsions are useful to improve precorneal residence time, drug corneal permeation, provide sustain drug release and thereby enhance ocular bioavailability. These preparations employ lipid additives such as soyabean lecithin and stearylamine as carrier systems for drugs to demonstrate better ocular performance. Emulsion behaves as a vehicle for drugs to slow down drug release, improve its chemical stability and precorneal residence time.

Examples: Gatifloxacin Eye Drop, Cyclosporin Eye Drop, Chloramphenicol Eye Drop, Prednesolone Eye Drop, Cationorm Eye Drop, etc.

Flurbiprofen Axetil Ophthalmic Emulsion

Flurbiprofen axetil	0.03%w/v
Castor oil	1.5%w/w
Tween-80	2%w/w
Purified water	5 mL

Method of preparation:

Flurbiprofen axetil ophthalmic emulsion is prepared by high-pressure homogenization with castor oil as oil phase and tween 80 as emulsifying agent.

Use: Anti-inflammatory

(3) Eye drop suspensions:

Suspension eye drops are nowadays mainly used for formulations involving steroidal drugs for treatment of ocular inflammatory diseases. In general when drug is not sufficiently soluble, it can be formulated as a suspension. Ophthalmic suspensions are formulated to improve stability, bioavailability, or efficacy of the water insoluble and unstable drugs. The drug and any other solid excipients suspended must be reduced to micro fine form. Usually 95% or more of the particles should have a diameter of 10 μm or less. The viscosity is maintained using polymer to retard settling of the insoluble particles when in container and to slow down rapid tear turnover rate when administered. Ophthalmic suspension products should have a "Do Not Freeze" warning on label because they are likely to agglomerate on freezing and will not resuspend by simple shaking. Ophthalmic suspensions contain solid particles dispersed in a liquid vehicle. They must be homogeneous when shaken gently and remain sufficiently dispersed to enable the correct dose to be removed from the container.

Sediment may occur, but this should disperse readily when the container is shaken, and the size of the dispersed particles should be controlled.

Examples: Natamycin Ophthalmic Suspension Eye Drop, Prednesolone Acetate Ophthalmic Suspension Eye Drop, Nepafenac Ophthalmic Suspension Eye Drop, Loteprednol Etabonate Ophthalmic Suspension Eye Drop, etc.

Prednesolone Acetate Eye Drop

Ingredients	**Quantity**
Prednesolone acetate	1% w/v
Dimethyl Sulfoxide + PVP K-30	1% w/v
Benzalkonium Chloride	0.01 – 0.02 % w/v
Edetate Disodium	0.005 – 0.1% w/v
Boric Acid	q.s. to buffer capacity
Sodium Borate	NMT 0.5%
Sodium Chloride q.s. to	308 mOsmol/kg
Polysorbate 80	0.1 – 3 %
HPMC 4000 cps	0.45 – 1.0 %
HCl / NaOH	q.s. to pH 5 – 6
Water for Injection	q.s. to required volume

Method of Preparation:

This preparation is prepared by dispersing sterile drug and excipients in the Water for Injection. The formulation is manufactured under aseptic conditions in clean room. This preparation has three phases namely buffer phase, slurry phase and polymer phase prepared as follows:.

(a) Buffer phase: Dispense 20 % batch size of Water for Injection in manufacturing vessel. Add all buffering agents to the Water for Injection and stir until clear solution is formed. This solution is filtered using 0.22 µm polyethersulfone (PES) or polyvinylidene fluoride (PVDF) or any other suitable filters.

(b) Slurry phase: Dispense 30 % batch size of Water for Injection in manufacturing vessel. Add insoluble drug into Water for Injection and stir until to get the homogeneous dispersion using homogenizer. The slurry obtained is again homogenized using high pressure homogenizer to reduce particle size.

(c) Polymer phase: Dispense 40 % batch size of Water for Injection in manufacturing vessel. Add polymer into Water for Injection and stir to get the homogeneous dispersion. This dispersion is sterilized by autoclaving at 121 °C for 30 min or filtered using 0.22 µm PES or PVDF or any other suitable filters.

The polymer phase is mixed with buffer phase and stirred for 10 min and then pH is adjusted to 6.4. This dispersion is mixed with slurry phase and stirred for 45 min the final volume of bulk suspension is made using Water for Injection and the bulk suspension is filled into eye drop containers, usually glass or plastics. These formulations may be sterilized by gamma radiation.

Use: Anti-inflammatory.

(b) Advantages of Eye Drops:

1. Solution eye drops are convenient to use.
2. Solution eye drops usually do not interfere with vision of patient.
3. Suspension eye drops have good patient compliance.
4. Suspension eye drops are best for drugs with slow dissolution.
5. Suspension eye drops has longer contact time.
6. Emulsion eye drops have prolonged release of drug from vehicle.
7. Eye drops offer moisture to eyes and used to deal with several eye related problems.

(c) Limitations of Eye Drops:

1. Solution eye drops undergo rapid precorneal elimination.
2. Solution eye drops need to be administered at frequent intervals.
3. Solution eye drops show non-sustained action.
4. Drug properties in suspension eye drops decide performance loss of particles.
5. Suspension eye drop has irritation potential due to particle size of the drug.
6. Emulsion eye drops causes blurred vision.
7. Improper use may of eye drops may lead to complications.

(d) Packaging of Eye Drops:

Eye drops are normally supplied in suitable multidose containers. The container should be fitted with a tamper-evident device. The maximum volume of the preparation in such a container should be no more than 10 mL. Droppers supplied separately should also comply with test for sterility. Ophthalmic drops may be provided in suitable single-dose containers to maintain the sterility of the contents and the applicator.

(e) Storage of Eye Drops:

Eye drop products should maintain their integrity throughout their shelf-life when stored at the temperature indicated on the label. Some products need to be stored in refrigerator whereas some at room temperature away from direct heat and light. Eyed drops are kept out of the reach and sight of children. They are stored in a cool and dry place.

(f) Quality Control Tests:

1. **Uniformity of volume:** For this test contents of eye drops from each container are poured completely into calibrated volume measures of the appropriate size to determine the volume of contents of 10 containers.
2. **Assay:** A specific and stability-indicating test is performed to estimate the concentration of drug in the eye drop product using suitable analytical method. In cases when the use of a non-specific assay test is justified, other supporting analytical procedures should be used to achieve overall specificity.
3. **Concentration of preservative:** Analysis of preservative concentration within these dosage forms is performed using suitable analytical method. The concentration of preservative must lie within the specified limit for the respective preservative.
4. **Preservative efficacy testing:** The efficacy of the preservative(s) within the eye drop formulations is assessed using the appropriate pharmacopoeial method.
5. **Appearance and clarity:** Clarity examination eye drops involves the visual assessment of formulation in suitable lighting on white and black background. It is performed for liquids and not for suspensions. Another method of clarity examination involves transmittance measurement using UV-V is spectrophotometer.
6. **The pH:** The pH of eye drops is most often determined using a potentiometric method and compared to the specified range. The optimum pH of eye drops must be equal to that of tear fluid, 7.4.
7. **Isotonicity:** Eye drops are subjected to isotonicity testing by mixing them with few drops of blood and observed under microscope at 45× magnifications and compared with standard 0.9% NaCl solution which depicts the isotonic nature. The shapes of blood cells are compared with standard 0.9% NaCl solution.
8. **Drop size:** The bottle cap is removed and bottle is inverted at 45° angle and pressed with finger to deliver a drop into the measuring cylinder. The step is repeated till solution in the measuring cylinder is filled up to 1 mL. The average weight of single drop, number of drops required for making volume 1 mL, and weight per mL of the solution is calculated. The drop size is calculated using the following formula:

$$\text{Drop size in } \mu L = \frac{\text{Average weight of drop (mg)}}{\text{Weight (g) per mL of solution under test}} \quad \ldots (5.10)$$

9. **Viscosity:** The viscosity of eye drops is measured using suitable viscometer such as Ostwald or Brookfield viscometer and compared to the range defined in the product specifications.
10. **Water loss:** To perform this test 30 bottles filled with exact volume of eye drop, plugged and capped properly are selected. The initial weight of each individual container is noted. The exact weight of each individual container after three months

stored at above-mentioned condition is determined. The percent water loss from the data obtained is calculated as follows:

$$\text{Water loss, \%} = \frac{\text{Average initial weight} - \text{Average final weight}}{\text{Density of liquid} \times 100} \times \text{Fill volume} \quad \ldots (5.11)$$

11. **Particle size:** This test is used for suspension eye drops. The particle size distributions of the dispersed drug within suspension formulations are determined using particle size analysis methodology.
12. **Drug release:** This test is used for suspension eye drops. Methods include bottle method, modified rotating basket method, diffusion method with the use of Franz cell, modified rotating paddle apparatus, or method with the use of flow-through device.

Other test performed on eye drops are sterility testing, preservative efficacy test, stability test, eye irritancy test as described under eye ointment.

5.8.3 Eye Ointments

Eye (ophthalmic) ointments are sterile, homogeneous, semi-solid preparations intended for application to the conjunctiva or the eyelids to treat eye problems. Once an eye ointment is applied to eye, the body temperature melts it to break into tiny drops. The molten mass hangs out between eyeball and eyelid giving the medicine time to work. Eye ointments are a safe to use but they might sting or make a sight blurry. Thus, eye ointment is directed to be used right before going to bed. It contains medicament(s) dissolved, suspended or emulsified in an ointment base. They are usually prepared from non-aqueous bases such as soft paraffin, liquid paraffin, and wool fat and may contain suitable additives, such as antimicrobial agents, antioxidants, and stabilizing agents. However, the greasy vehicles have drawbacks of their poor tolerance, greasiness, vision blurring effect, etc.

The amount of finely divided solid (drug) released in unit time is a function of concentration, solubility in ointment base, and diffusibility of the drug in the base. Certain proprietary formulations of eye ointments available in single-dose container take the form of an elongated, flexible gelatin capsule with one end constricted, and are opened by cutting off the constricted end with sterile scissors. Ophthalmic ointments should be of uniform consistency. When a sample is rubbed on the back of the hand, no solid components should be noticed.

(a) Methods of Manufacturing:

Eye ointments are prepared aseptically by incorporating the sterile medicament(s) into a sterile base. These ointments are primarily anhydrous and the base consists of mineral oil and white petrolatum. The proportion of these bases can be varied to adjust consistency and the melting point.

There are two methods of incorporating the drugs in ointment bases while maintaining aseptic conditions throughout the process.

(1) **Water soluble medicaments:** Drug is dissolved in minimum volume of purified water; the solution is then sterilized by autoclaving or filtration and gradually incorporated in the previously melted sterile base which is stirred until cold.

Example: Atropine Eye Ointment, Hyoscine Eye Ointment, etc.

(2) **Insoluble medicaments:** Drug is finely powdered and triturated with a small quantity of the melted, previously sterilized base. The mixture is then incorporated with the remainder of the melted base.

Examples: Chloramphenicol Eye Ointment, Hydrocartisone Acetate Eye Ointment, etc.

Do you know?
Ophthalmic products includes: Eye drops, Eye lotion, Eye ointment, Eye suspension and Contact lens solution.

(b) Formulation of Eye Ointment:

The ointment base used in preparing ophthalmic ointments must be non irritant and should melt near to the body temperature, so as to permit the diffusion of the drug through the lachrymal secretion of the eye. For preparation of Atropine eye ointment following sterile ointment base is used:

Sterile Ointment Base:

Yellow soft paraffin	80 g
Liquid paraffin	10 g
Wool fat	10 g

Preparation of Base: To prepare sterile ointment base melt wool fat and yellow soft paraffin on water bath and to molten mass add liquid paraffin. Filter through Whatman 54 filter paper, placed in a heated funnel. Sterilize the molten base at 160 °C for 2 hours. Wool fat is used to ensure specific emulsification of the solution and help in absorption of drug. Liquid paraffin is used to reduce viscosity of base, so that it can be easily expelled from collapsible tube and applied to the eye.

Atropine Eye Ointment

Atropine sulfate I.P.	1 g
Sterile ointment base	100 g

The atropine sulfate is incorporated in sterile ointment base, mixed well to obtain uniform mass and packaged in the sterile container. The ointment is packaged in small, sterilized tamper-evident collapsible aluminium or polyvinyl chloride tube.

(c) Advantages:

(1) Eye ointments offer longer contact time and greater total drug bioavailability.

(2) They have flexibility in drug choice.

(3) They show improved drug stability.

(4) Eye ointments show better bioavailability than eye drops.

(5) Eye ointments have no tear dilution.

(d) Limitations:

(1) Eye ointments may interfere with the vision and may stick eyes lids.

(2) Eye ointment has poor patient compliance.

(3) They have slower onset of action and takes longer time for peak absorption.

(e) Storage:

These products should be stored to maintain their integrity throughout their shelf-life at the temperature indicated on the label. Some products are stored in refrigerator whereas some at room temperature away from heat and light.

(f) Quality Control Tests:

(1) Assay: The strength of drug in sterile formulation is determined using suitable method specified under monograph. The concentration of drug must lie within 95–105% of the nominal concentration.

(2) Concentration of preservative: Analysis of preservative concentration within sterile preparations is determined using suitable analytical method as specified in monograph and must comply with it.

(3) Preservative efficacy test: The efficacy of the preservative(s) within the eye ointment is tested using appropriate pharmacopoeial method using test organisms specified.

(4) Sterility testing: The assessment of sterility of ophthalmic products is performed using pharmacopoeial methods using thioglycollate medium over period not shorter than 14 days. Examination of sterility involves inspection of inoculated sample for growth of aerobic and anaerobic bacteria, and aerobic bacteria and fungi.

(5) Metal particles in eye ointments: The presence of metal particles in ophthalmic eye ointment is determined by completely extruding the contents of 10 tubes. The sample is transferred into separate, clear, flat-bottom, 60 mm Petri dishes and heated at 85 °C for 2 h and then cooled to room temperature to solidify. Petri dish is inverted and on the stage of a suitable microscope to examine for metal particles. The number of metal particles of size 50 µm or larger are counted. The sample pass the test if the total number of such particles in all 10 tubes does not exceed 50, and if not more than 1 tube is found to contain more than 8 such particles.

(6) Eye irritancy test: Eye irritation by eye ointment is determined by Draize eye test. For the test, eye ointment is applied directly on the cornea 3 to 6 albino rabbits. Left eye ball is used as a control and right eye ball for test sample. After introducing an ointment, the eyelids are kept closed for a few seconds. Eyeball condition is observed before and after introducing the formulation. The evaluation is conducted at time interval of 1 h, 24 h, 48 h, and 72 h from introducing samples. Ocular changes

may be assessed using a scoring system, in which every change in the area of eyelid, conjunctiva, cornea, and iris is scored.

In addition to above tests, other quality control tests used include uniformity of weight, viscosity, particle size, drug release, stability test, etc.

5.9 IMMUNOLOGICAL PRODUCTS

The immune system is a host defense system comprising many biological structures and processes within the living body. Immunology is the study of immunity, which is the capacity of the body to defend against infection. If the immune system is not functioning as it should, it can result in disease, such as autoimmunity, allergy, cancer, etc. Immunization is the process whereby a person is made immune (resistant) to an infectious disease, typically by the administration of a vaccine.

Infection is said to be occurred when microbes invade the human body. The disease produced by microbes is known as infection. The infection may be caused by physical contact with diseased person or animal, through droplets containing microbes expelled from respiratory tract, environmental dust containing microorganisms, contact with contaminated objects and hands, and arthropod vectors. The ability of microorganism to cause infection depends upon virulence, the number of microorganisms, route of entry and the resistance of the host. Immunity is defined as the ability of an organism to resist a particular infection or toxin by the action of specific antibodies or sensitized white blood cells. It is the resistance offered to disease by individual.

Immunity is classified into to natural immunity and acquired immunity.

(1) **Natural (Innate) immunity:** It is the immunity in which antibodies generated due to a normal infection. It includes antibodies provided by mother through their colostrums and the initial breast milk. This immunity only protects for short time, but when infant is most vulnerable.

(2) **Acquired immunity:** When natural immunity is insufficient to protect the body against many microbial infections, an additional immunity is acquired either actively or passively.

(i) **Active immunity:** Active immunity can be acquired by natural disease or by vaccination. Vaccines stimulate production of antibodies and other components of the immune mechanism. They consist of either:

1. A live attenuated form of a virus: Measles (mumps and rubella vaccine) or bacteria [Bacille Calmette-Guerin (BCG) vaccine] or
2. Inactivated preparations of the virus or bacteria: Influenza vaccine or
3. Detoxified exotoxins produced by the micro-organism: Tetanus vaccine, or
4. Extracts of a micro-organism: Organism (pneumococcal vaccine) or Recombinant DNA technology (hepatitis B vaccine).

Active immunization stimulates the host's immune system to produce specific antibodies or cellular immune responses or both which protect against or eliminate a disease.

(ii) Passive immunity: It is the immunity with immediate protection against certain infective organisms. It can be obtained by injecting preparations made from the plasma of immune individuals with adequate levels of antibody to the disease under consideration. The duration of this immunity depends upon the dose and the type of immunoglobulin. Passive immunity may last only for few weeks; and when necessary, passive immunisation can be repeated. Antibodies in human are termed as immunoglobulins while those prepared in animals are called antiserum.

(iii) Artificial immunity: Artificial immunity is induced by immunization by giving a vaccine or immunoglobulin. Vaccination means administration of a vaccine to help the immune system develop protection from a disease. The immune response may be humoral or cell-mediated.

(iv) Humoral immunity: Humoral immunity is based on serum antibodies that are produced by plasma cells and bind to antigens in order to assist with their elimination.

(v) Cell-mediated immunity: This immune depends on antigen recognition and lymphocyte responses to destroy infected cells and prevent organisms replicating within cells.

Definition:

Immunological products can be defined as the proprietary delipidation-based methods and systems for the production of treatments for viral or bacterial infections. These products are the preparations used for the prevention of diseases (vaccines) or for the treatment of diseases (antitoxin and antiserum) or for the diagnostic purposes (bacterial toxins). These are biological products of proteinous nature except poliomyelitis vaccine. Majority of immunological preparations are administered by parenteral routes as they become inactive when administered by oral route. The exception is poliomyelitis vaccine, which is administered by oral route. The immunological products can be classified on the basis of their use as shown in Fig. 5.10.

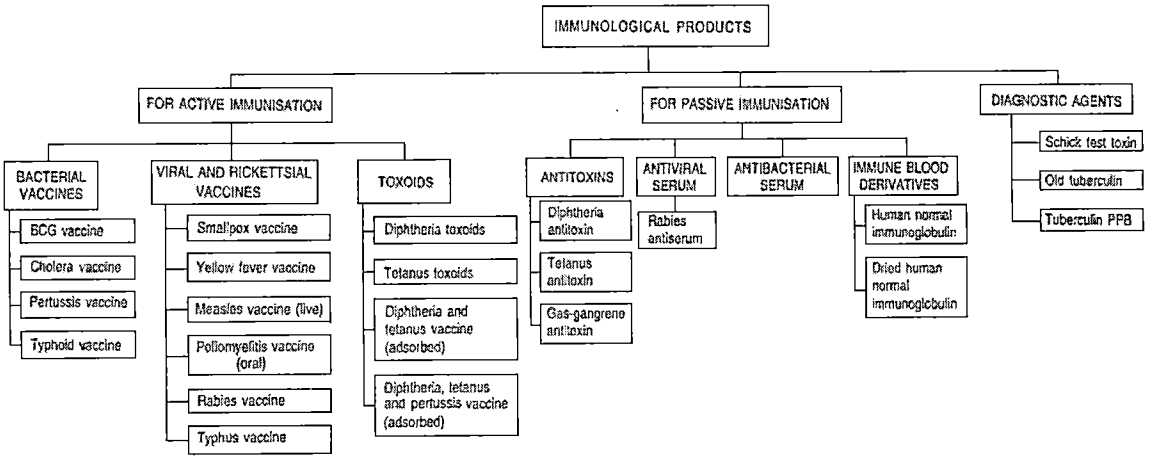


Fig. 5.10: Classification of Immunological Products

Do you know?

- The term immunology was coined by Russian biologist Ilya Ilyich Mechnikov, who received the Nobel Prize for his work in 1908.

5.9.1 Sera

Sera, also called as blood serum, is a clear yellowish fluid obtained upon separating whole human blood into its solid and liquid components once it has been allowed to clot. The plasma of an immune person or animal contains a large number of antibodies that are found in the serum that separates. Serum is the liquid part of the plasma that does not contain fibrinogen, blood cells, bacteria or toxins and remains as fluid after clotting of blood. It contains antibodies formed in another animal. Sera acquire immune immediately that remains for a short time. A specific animal is immunized and its whole blood is collected and the serum is separated upon centrifugation. A serum may contain anti-toxic, antibacterial or antiviral antibodies and, accordingly, is called an antitoxic, antibacterial of antiviral serum. Antitoxic sera, however, are more often known as antitoxins. Anti-toxic sera are more effective than anti-viral, anti-bacterial. Most antisera are obtained from animals in which active immunity has been stimulated artificially. The exception is German measles that cannot be reproduced in animals and thus, human serum or products derived from it are used.

(a) Diphtheria Antitoxin:

It is sterile, non-pyrogenic solution containing specific antitoxic antibody from healthy horse. It neutralizes the toxins produced by Corynebacterium diphtheriae. The C-diphtheriae is a pathogenic bacterium that causes diphtheria. For diphtheria antitoxins, a toxoid is used. The horses are immunized at the start by toxoid and after few months it ends with toxin. The immunity of such susceptible horses is so strong that they can be immunized with multiples of lethal dose to obtain antigen. Diphtheria Antitoxin is prepared by hyperimmunizing horses with diphtheria toxin. Blood plasma obtained from the hyperimmunised horses is rich in antibodies to diphtheria toxin.

1. **Prophylactic use:** The use of diphtheria antitoxin is not recommended for prophylaxis as its protective effect lasts only for 1 to 2 weeks. Additionally, it may cause sensitization to horse sera.
2. **Therapeutic use:** A dose of 10,000 to 30,000 IU of diphtheria antitoxin may be injected intramuscularly (I.M.) in mild to moderately severe cases of diphtheria and up to a maximum of 1,00,000 IU in severe cases after testing for serum sensitivity.

In some cases symptoms such as itching urticarial rash, pains in joints and muscles, fever, enlargement of lymph glands appear 7-12 days after the injection of diphtheria antitoxin. These should be treated with antihistamines and corticosteroids. Usually these symptoms of serum sickness last a few days and the patients recover without any complications.

Packing: Diphtheria antitoxin: 10,000 IU in 10 mL vials

Diphtheria vaccine: 10,000 IU in 5 mL vials

(b) Tetanus Antitoxin:

Tetanus Antitoxin is used for prophylaxis and treatment of Tetanus. It contains specific antitoxic antibody which neutralize the toxin produced by Clostridium Tetani. This antitoxin is also recommended to be used in case of surgical operations involving reopening of old scars, piles and fistulae. It is administered either subcutaneously (S. C.) or I. M. with each dose of 1.0 mL. Its method of preparation, storage and dose are similar to diphtheria antitoxin.

1. **Prophylactic use:** It is given to the persons at risk with infected wounds, wounds contaminated with soil or mud, deep or punctured wounds and wounds with devitalizing tissue damages. A dose of 1,500 IU should be given by S. C. or I. M. route as early as possible after the wound is received. In severe wounds, the dose may be doubled or tripled and the antitoxin injected in two or three places around the wound.
2. **Therapeutic use:** For therapy, large doses 100,000 - 200,000 IU of antitoxin are given very slowly by I. V. route followed by smaller weekly doses I. M. as required. Some physicians prefer a smaller initial dose of 20,000 IU by I. M. route. Active immunisation may be initiated when the patient is cured of the illness.

Packing: It is packed in the range of 1,500 IU in 1 mL to 50,000 IU in 12.5 mL single vial.

(b) Botulinum Antitoxin:

Botulinum antitoxin, also known as botulism antitoxin, is comprised of antibodies or antibody antigen-binding fragments that block the neurotoxin produced by the bacterial species Clostridium botulinum. Botulinum toxin causes botulism, a paralytic syndrome characterized by symptoms of descending symmetric muscle weakness. Symptoms can include blurry vision, inability to speak or swallow, and weakness in the bilateral upper extremities with progression to the chest and lower extremities. Botulinum toxin is the most poisonous substance known with the lethal dose of 1 ng/kg. In adults, the most common form of transmission is food-borne botulism where the toxin itself is ingested. In wound botulism, it enters through bacterial spores, and toxin is produced locally. Another form is infant botulism which occurs when young children (below the age of 1-year-old) ingest C. botulinum. This can generate botulism in the immature GIT and cause a "floppy" baby.

Mechanism of Action: Botulinum toxin binds irreversibly to presynaptic nerve endings at neuromuscular junctions. Through receptor-mediated endocytosis, the toxin enters the cell and cleaves SNARE proteins, which are necessary for the release of acetylcholine into the synaptic cleft. Blockade of voluntary motor and autonomic cholinergic junctions led to xerostomia (dry mouth), blurry vision, diplopia, dysphonia, dysarthria, dysphagia, and muscle weakness. The most concerning clinical manifestation is when blockade affects respiratory muscles leading to respiratory failure. Botulinum antitoxin works by binding botulism toxin in the blood. The polyclonal antibody fragments bind free botulinum toxin, which then prevents the toxin from being internalized at the post-synaptic cholinergic receptor. Because antitoxin only binds free botulinum toxin, it prevents the progression of symptoms.

Administration: Prior to the administration of Botulinum antitoxin, a skin test is performed to evaluate for hypersensitivity. Patients who are at high risk for hypersensitivity should be given this antitoxin at less than 0.01 mL/min. It is packed in a vial that must be thawed and prepared prior to administration. If the vial is frozen upon receiving it from the Center for Disease Control and Prevention (CDCP), there are two ways of thawing the contents. In first method it is placed in the refrigerator at 2 to 8 °C for about 14 h and in second method it is placed at room temperature for 1 h and then in a water bath at 37 °C.

Precautions: Once thawed, the antitoxin may not be refrozen. Do not use if the vial has discoloured or turbid fluid and look for particles other than a few translucent-to-white proteinaceous particulates. As soon as the vial is opened, anti-toxin must be used as quickly as possible. Do not shake the vial. Discard any excess antitoxin.

(c) Gas Gangrene Antitoxin:

Gas gangrene is a rapidly progressive, potentially fatal condition characterized by widespread necrosis of the muscles and subsequent soft-tissue destruction. This is a dreaded consequence of inadequately treated missile wounds, crushing injuries and high-voltage electrical injuries. Gas gangrene is polymicrobial in nature. The causative agent is Clostridium species (spore forming, gram positive), for example, Clostridium welchii, Clostridium oedematiens and Clostridium septicum.

Symptoms: The symptoms include high fever, shock, massive tissue destruction, blackening of skin, severe pain around a skin of wound, blisters with gas bubbles form near the infected area, the heartbeat and breathing become rapid. The infection spreads quickly due to invasive abilities possessed by the toxins or their associated enzymes.

The name gas gangrene disease is due to the large amount of foul-smelling gas that collects in the tissues and helps to disintegrate them. The antitoxins made from Clostridium species are official in Pharmacopoeia. The most potent toxin produced by each species is known as the α-toxin and is present in the antigen used for immunizing the horse. Sometimes two antitoxins are produced in the same animal. The mixed antitoxin is preferred because antitoxin treatment must start as early as possible and there is rarely time for bacteriological identification of the organism responsible for the infection. Best results follow I. V. injection but precautions are essential to prevent serum shock. Occasionally, the triple product is used to provide prophylaxis after serious injuries but antibiotics are increasingly preferred for this and for therapeutic purposes.

5.9.2 Vaccines

Vaccine is defined as an antigenic substance, prepared from the infectious microorganisms or a synthetic substitute, used to provide immunity against one or several diseases. Vaccines stimulate the body to make antioxidants. Vaccines are administered to induce in the recipient specific and active immunity against infectious microorganisms or toxins produced by them. They contain living or killed microorganisms, bacterial toxoids or

antigenic material from the particular parts of bacterium, rickettsia, or virus. There are two types of vaccines:

(i) **Live attenuated vaccines:** These vaccines produce longer-lasting immunity, similar but less than that produced by natural infection. One dose gives long-lasting immunity. However, they are inherently less stable.

Examples: Measles, Mumps, Rubella, Rotavirus, and Tuberculosis vaccines.

(ii) **Inactivated vaccines:** This vaccine usually requires a series of primary vaccinations followed by boosters. Some of these vaccines have adjuvants (for example, aluminium hydroxide, aluminium phosphate) to enhance the antibody response. There is no risk of person-to-person spread, and the vaccines are more stable.

Examples: Hepatitis A and some influenza vaccines.

Side-effects: Some vaccines commonly produce a mild reaction.

(a) Bacterial Vaccines:

Bacterial vaccines are either sterile suspension of live or killed bacteria or sterile extracts of derivatives of bacteria. They may be simple (prepared from one species or variety) or mixed (mixtures of two or more simple vaccines) and univalent (prepared from one strain) or polyvalent (prepared from more than two strains).

(1) Vaccine prepared from cultures:

Bacterial vaccines may be prepared from cultures grown on solid or liquid medium. The bacteria are suspended in normal saline solution or freeze dried. Vaccines containing living bacteria may be prepared from strains which are avirulent for man but which can stimulate the production of antibodies active against pathogenic strains of the same species. The bacterial vaccines must be free from any substance which is toxic, allergic or exhibit other undesirable immunological reactions in man.

BCG Vaccine: Freeze-dried BCG vaccine is in the form of white pellet which when reconstituted yields an opalescent suspension. It contains live culture of the bacillus Albert Calmette and Camille Guerin strain of Mycobacterium tuberculosis.

Preparation: The bacilli are grown on a suitable culture media. When 1 mg of bacilli plated out on suitable solid culture media, shows not less than 20 million colonies. They are grown for not more than 14 days. After a suitable growth, they are separated by filtration in the form of a cake. The cake is homogenized in a grinding flask and suspended in a suitable sterile liquid medium designed to preserve the antigenicity and the viability of the vaccine. The suspension is transferred into the sterile vials and freeze-dried. BCG vaccine contains no antimicrobial agent.

Storage: It is store in hermetically sealed light resistant glass containers at 2 – 8 °C. The reconstituted vaccine must be used immediately after its preparation.

Use: As immunizing agent to provide protection against tuberculosis.

Dose: Prophylactic, 0.1 mL as a single dose by intracutaneous injection.

(2) Vaccine prepared from killed microorganism:

These vaccines may be prepared by killing the microorganism by chemical or physical means with preserving antigenic potency of the vaccine.

(i) Cholera: Cholera is an intestinal infection caused by the spirillum Vibrio cholerae that causes profuse diarrhea. The cholera vaccine is used for travelers to certain tropical countries, where the disease is endemic. Protection provided by this vaccine is only for short time (six months). The antigenicity of this vaccine depends on use of appropriate strains. A less severe form of cholera is widespread in the Far East caused by eltor variants. Pharmacopoeia includes Eltor vaccine prepared from eltor. A mixed preparation containing Cholera and Eltor vaccines as well as a mixture of cholera and TAB vaccines is also available.

(ii) Pertussis: Whooping cough is caused by Bordetella pertussis at childhood. This is because babies may not receive pertussis antibodies from their mothers. This disease can also be caused by several antigenically-different strains of this organism. Therefore, to provide high level protection all these strains can be included in the vaccine. The abnormal toxicity can be eliminated by use of cold storage for up to 3 months. This vaccine is used in the form of triple or quadruple antigen in which it has an adjuvant effect.

(iii) Plague: Plague is caused by Pasteurella pestis which is transmitted to man by the rat flea. This vaccine is used for protecting service personnel posted to areas where plague is endemic and for special groups of workers such as those engaged in research on biological warfare. Immunity persists for short time and re-immunisation is needed at 6 months intervals. This vaccine preparation possess maximum amount of capsular antigen.

(iv) TAB and TABC: These mixed polyvalent vaccines are used in the prophylaxis of enteric infections. TAB vaccine is made by mixing simple vaccines of Salmonella typhi, *S. paratyphi A and S. paratyphi B.* TABC vaccine is made from mixing TAB vaccine with vaccine of *S. paratyphi C.* The *S. typhi* and *S. paratyphi* C have the Vi antigen that increases the virulence of the cells. They are more resistant to phagocytosis. There are two method of preparing these vaccines. In the first, the bacteria are destroyed by heat, and phenol is used as the preservative in the final preparation. In the other, the organisms are killed by exposure to 75 %v/v alcohol and the preparation is preserved with 25%v/v alcohol. These vaccines reduce the risk of typhoid fever by 75 %.

Immunity is most likely to break down when the body is exposed to heavy infection through food. Protection is for short term and re-immunisation is needed after 6 months to a year. TAB can also be used in mixed form with tetanus vaccine (TABT vaccine) and with cholera vaccine (TAB and Cholera vaccine). In the mixture containing tetanus vaccine the bacterial cells potentiate the antigenic activity of the toxoid.

(b) Viral Vaccines:

Viral vaccines are used in the prevention of viral infections. These vaccines contain either attenuated (alive but cannot cause disease) viruses or inactivated viruses. Attenuated vaccines include the live form of the virus. These viruses induce an immune response.

Inactivated or killed viral vaccines include viruses that have lost their ability to replicate. To cause immune reaction, it contains more antigens. The vaccines that induce active immunity are those that contain killed virus or those that contain live virus whose pathogenicity has been attenuated. Vaccines that contain purified viral proteins are often called subunit vaccines, for example, hepatitis B vaccine. The subunit vaccine resembles to those of killed vaccines but has no viral replication in these vaccines.

(1) From free-living animals:

(i) Smallpox vaccine: Smallpox was a serious infectious disease caused by the variola virus that spread from one person to another. People who had smallpox had a fever and a distinctive, progressive skin rash. Smallpox was eradicated, and no cases of naturally occurring smallpox have happened since 1977. Smallpox can be prevented by the smallpox vaccine, also called vaccinia virus vaccine. This vaccine is made from a virus called vaccinia, which is a poxvirus similar to smallpox, but less harmful.

(ii) Rabies vaccine: Rabies is mainly a disease of animals. Humans get rabies when they are bitten or scratched by infected animals. Rabies infects the central nervous system. At first there might not be any symptoms but weeks or even months after a bite, rabies can cause weakness or discomfort, fever, or headache and as the disease progresses, the person may experience delirium, abnormal behavior, hallucinations, hydrophobia, and insomnia. Rabies can be prevented by vaccinating pets.

The rabies vaccine was developed by Louis Pasteur. It was prepared from animal nerve tissue to embryonated eggs, from rabies virus using cultures of human diploid cells, from explants cells of hamster, dog or fetal calf kidney, fibroblasts of chicken embryo, or diploid cells from rhesus monkey fetal lung, and cells from continuous lines (Vero cells). Following are the most commonly used rabies vaccines today:

1. Vaccine for humans prepared in human diploid cells
2. Purified Vero cell vaccine for humans
3. Purified chick-embryo cell vaccine for humans

(2) From fertile eggs:

Some viruses grow well in the specific part of the embryo. These viruses can be inoculated either on to the chorioallantoic membrane, into the embryo, into the yolk sac, or into the allantoic fluid.

(i) Smallpox vaccine: The egg is incubated for 3 days and then egg shell is removed aseptically. The thickened and infected chorioallantoic membrane is separated in saline. It is then frozen and ground to free the viruses. This is followed by diluting the suspension with diluent.

(ii) Yellow fever vaccine: This vaccine contains attenuated strains of yellow fever virus of strain 17D. This strain is obtained from Asibi strain by numerous passages through tissue cultures. First, it is cultured in mouse embryo cells and then in chick embryo from which the central nervous tissues are removed. As this virus is living it produces strong and long-

lasting immunity which may last for 10 years after injection. This vaccine is deteriorated due to water and thus it must be administered within half an hour once reconstituted.

(iii) Influenza vaccine: Influenza disease is caused by Type A or Type B viruses. The Type A virus has widespread outbreaks while Type B virus has localized outbreaks. An influenza vaccine is given with a needle, usually in the arm. Seasonal vaccination protects against the 3 or 4 influenza viruses that are most common during the season. There are three types of influenza vaccines namely; inactivated influenza vaccine [IIV], recombinant influenza vaccine [RIV], and live attenuated influenza vaccine (LAIV). There is no preference while selection for any of these vaccines over another.

Do you know?

- SARS-CoV-2 virus causes COVID-19.
- Vaccines available to treat COVID19 are:
  - Covishield (Serum Institute of India Pune)
  - CoWaxin (Bharat Biotech Hyderabad)
  - Covid-19 (Johnson & Johnson USA)
  - S-putnik V (Russia)
  - Spikevax (Moderna)

(3) From tissue culture:

(i) Poliomyelitis vaccine:

Poliomyelitis is an acute communicable disease of humans caused by a human enterovirus of the Picornaviridae family. Poliovirus is transmitted from one person to another by oral contact with secretions or faecal material from an infected person. Most poliovirus infections are asymptomatic but upon incubation over 7–10 days, about 24% of those infected suffer from fever, headache and sore throat. There are three serotypes of poliovirus with each being antigenically distinct. The vaccines available are an inactivated polio vaccine (IPV) and a live attenuated oral polio vaccine (OPV). The presence of neutralizing antibody against polioviruses provides protection against poliomyelitis. The immunity induced by one serotype does not provide protection against the other two serotypes.

Inactivated polio vaccine: IPV is produced from wild-type poliovirus strains of each serotype that have been inactivated with formalin. As an injectable vaccine, it can be administered alone or in combination with other vaccines such as diphtheria, tetanus, pertussis, hepatitis B, and haemophilus influenza.

Oral polio vaccine: OPV consists of a mixture of the three live attenuated poliovirus serotypes (Sabin types 1, 2 and 3). Trivalent OPV (tOPV) is used for routine or supplemental vaccination, monovalent OPVs is used against serotype type-1 (mOPV1) and type-3 (mOPV3).

(ii) Measles vaccine:

Measles is a contagious disease caused by a virus. It spreads through the air when an infected person coughs or sneezes. Measles starts with a cough, runny nose, red eyes, and fever. Then a rash of tiny, red spots breaks out. It starts at the head and spreads to the rest of the body. Measles can be prevented with MMR vaccine that provides protection against measles, mumps, and rubella (MMR). The children are administered with two doses of MMR vaccine. The first dose is given at 12 - 15 months of age, and the second dose at 4 - 6 years of age. The MMR vaccine is very safe and effective. Children are administered with MMR vaccine, which protects them against measles, mumps, rubella, and varicella (chickenpox).

(c) Rickettsial Vaccine:

Rickettsiae are small bacteria which grow and multiply in living cells. Most rickettsial organisms are transmitted by the bites or infectious fluids inoculated into the skins from fleas, lice, mites, and ticks and also through inhalation of bacteria or inoculating conjunctiva with infectious material. Rickettsial infections are typhus fever, and the Rocky Mountain spotted fever. The only official rickettsia vaccine is Typhus prepared from the organisms grown in the yolk sac of the fertile egg.

Typhus vaccine: The epidemic typhus is caused by *Rickettsia prowazeki* and *Murine typhus* by *R. typhi*. The mortality rate is high in epidemic typhus, whereas Murine typhus is milder. Vaccines are useful in providing protection against both these forms of typhus in endemic areas. The typhus vaccine is prepared using embryos that have died or become moribund; the heavily infected yolk sacs are removed and ground to liberate the rickettsiae. The ground material is suspended in an isotonic solution containing 0.2 to 0.5 % of formaldehyde to kill the organisms. It is inactivated to avoid severe reactions. At this stage the preparation contains 10 - 15 % of yolk sac material. To reduce its hazard potential it is treated with ether or trichlorotrifluoroethane. The aqueous phase is separated and used as the vaccine. Thiomersal may be added as a bactericide. R. prowazeki liberates soluble antigen into the yolk sac thus care is taken to retain it in the preparation.

Typhus vaccine can also be obtained from free-living animals, for example, from the lungs of mice that have been infected intranasally with massive doses of typhus rickettsiae to give them typhus pneumonia and from the intraperitoneal fluid of gerbils (North African rodents) infected by intraperitoneal injections of rickettsiae.

Do you know how vaccines are developed?

Each vaccine under development must undergo ....

- Screenings and evaluations to determine which antigen should be used to invoke an immune response. This preclinical phase is done in animals to evaluate its safety and potential to prevent disease.
- If the vaccine triggers an immune response, it is then tested in human clinical trials in three phases namely; Phase I, Phase II and Phase III.

5.9.3 Toxoids

Some bacterial infections such as diphtheria and tetanus are caused not by the bacteria themselves but by the toxins they secrete. Toxoid vaccines are produced by harvesting a toxin produced and altering it chemically, usually with formaldehyde (formalin), to convert to a toxoid. This treatment destroys toxic properties without significant loss of antigenicity. The formaldehyde attacks toxic groups without affecting antigenic active sites. The toxoid is then purified. Toxoid vaccines induce antibodies that neutralize the harmful exotoxins released from these bacteria. Toxoids are inactivated toxins and are vaccines directed at the toxins produced by a pathogen. The tetanus and diphtheria toxoids have long been part of the standard childhood immunization series. They require a series of injections for full immunity, followed by boosters every 10 years.

(a) Diphtheria Vaccine:

Diphtheria is a toxoid vaccine against diphtheria, an illness caused by Corynebacterium diphtheriae. It creates a thick coating of dead tissue in the throat or nose, which makes it hard to breathe and swallow. Other symptoms include weakness, sore throat, swollen glands in the neck and fever. Serious cases of diphtheria can damage the heart, kidney, and nerves. It also can cause paralysis, pneumonia, and lung failure. It can be so deadly for certain age groups that 1 in 10 people will die from diphtheria even with treatment. Getting vaccinated is the best way to prevent diphtheria.

Diphtheria vaccine is used to be a common cause of both illness and death for children. Diphtheria toxoid-containing vaccines protect nearly all people (95%) for approximately 10 years. Babies and children younger than 7 years old receive DTaP or DT, while older children and adults receive Tdap and Td. Protection decreases over time, so adults need to get a Td or Tdap booster shot every 10 years to stay protected.

1. Infants and children: Dose of the vaccine at 2, 4, 6, 15 and 18 months and 6 years.
2. Preteens and teens (age 7 to 18): Older children need 1 booster shot of the Tdap vaccine at age 11 or 12 as part of their routine vaccine schedule.
3. Adults: Adults need 1 booster shot of the Td vaccine every 10 years as part of their routine vaccine schedule.
4. Pregnant women: Pregnant women need 1 booster shot of the Tdap vaccine during the third trimester of each pregnancy.

There are four vaccines that provide protection against diphtheria:

1. **DTaP vaccine:** Protects young children from diphtheria, tetanus, and whooping cough.
2. **DT vaccine:** Protects young children from diphtheria and tetanus.
3. **Tdap vaccine:** Protects preteens, teens, and adults from tetanus, diphtheria, and whooping cough.
4. **Td vaccine:** Protects preteens, teens, and adults from tetanus and diphtheria.

Do you know?

- Toxoids used in modern vaccines are commonly obtained by incubating toxins with formaldehyde at 37 °C (98.6 °F) for several weeks.

Preparation of Toxin:

A suitable strain of Corynebacterium diphtheriae is grown on a liquid medium. After incubation under optimal conditions until toxin production has reached a satisfactory level, the bulk of the organisms are removed on paper pulp and the filtrate is sterilized using fibrous pads or ceramic candles. Formaldehyde solution is added and the mixture incubated at 37 °C until the toxicity has been removed over the period of 2-3 weeks. The resulting material is known as Formol toxoid (FT). It is purified to make the products relatively free from side effects but is weaker prophylactic and less stable.

(i) Toxoid-antitoxin floccules (TAF): The reactions caused by crude FT are caused by broth constituents and metabolic products of the organism. When appropriate portions of toxoid and antitoxin are mixed, floccules are obtained that contain almost all of the antigenic activity. Upon separation and washings they are made free of contamination and the product is called as TAF. It is of much significance for adults sensitive to the reaction-causing components of immunological preparations. Since it is a weaker antigen, its three doses must be given. As TAF contains diphtheria antitoxin, it has a least risk of sensitization. A neutralized product has significant activity because neither toxoid nor antitoxin is damaged when they combine. The combination dissociates under suitable conditions, after the floccules have been injected into the body, leaving the toxoid free to stimulate antibody production. It is prepared by adding 80 units of antitoxin to 100 units of toxoid, wherein the toxoid is slightly under-neutralized. After leaving for about 3 weeks to allow the floccules to form and settle, the supernatant liquid is decanted. The floccules are washed with saline, by decantation, until the washings are colourless, and resuspended in saline containing a bactericide.

(ii) Alum Precipitated Toxoid (APT): APT preparation is a pure toxoid that slowly absorbed from the site of injection and also slowly excreted from the body that has higher antigenic activity. It is prepared by treating high quality formol toxoid with charcoal to remove colouring matter, and some of the non-specific non-toxoid impurities which may cause reactions. A charcoal is separated by filtration followed by addition of suitable concentration of alum. Alum reacts with impurities (bicarbonate, phosphate and protein) in the toxoid and produces a precipitate that contain aluminium hydroxide and phosphate on which the toxoid is adsorbed. The precipitate is washed and suspended in saline containing a bactericide that provides a depot (due to insolubility) in the tissues from which the antigen is slowly released to give a prolonged stimulus. Alum, which potentiates the effect of antigen, is called adjuvant. APT as it produces much higher antibody levels, two doses are sufficient. It is free from sensitizing horse protein and contains toxoid of improved purity.

(iii) Purified Toxoid Aluminium Phosphate (PTAP): PTAP contains a much purer form of toxoid. It is obtained by using a semi-synthetic medium in the preparation of the toxin.

It excludes much of the non-specific material as possible. It can also be obtained by a purification of the toxoid using magnesium hydroxide. It helps to precipitate colour, phosphate, some proteins, and ammonium sulphate and cadmium chloride. The separation helps to reduce the possibility of reactions. It also removes the impurities that give a precipitate with alum. Thus, it is necessary to use a preformed carrier such as pure hydrated aluminium phosphate. PTAP is an excellent antigen due to its depot effect. This toxoid is very pure and can be freeze-dried producing batches of uniform potency.

Purified toxoid aluminium hydroxide (PTAH) is similar preparation to that of PTAP wherein aluminium phosphate is replaced with aluminium hydroxide.

(b) Tetanus Vaccine:

Tetanus vaccine is prepared from the exotoxins of the anaerobe Clostridium tetani. The activity of purified tetanus vaccine is increased by administration with killed organisms. This form is used in combined prophylactics containing microbial suspensions. A mixed vaccine is used to protect servicemen against typhoid and paratyphoid fevers, and tetanus. This preparation requires control of media composition in toxoid production.

(c) Staphylococcus Toxoid:

Staphylococcus toxoid is made from the exotoxins (α-toxin) of staphylococcus aureus. It is occasionally given to susceptible individuals to prevent boils and other recurring local staphylococcal infections. There is only one form, a formol toxoid. Unlike the corresponding diphtheria and tetanus preparations, it is not obligatory to remove completely the specific toxicity of the toxin during toxoiding but it must be reduced to a low level at which certain dangerous properties of the α-toxin have been destroyed. That means its ability to cause haemolysis of RBCs, necrosis of the skin, and death of rabbit after I.V. injection is lowered. Occasionally, autogenous vaccines are made from *Staphylococcus aureus*. These vaccines contain organisms freshly isolated from the patient who is to receive the vaccine.

(d) Formulation of Vaccines:

Other than microorganism or its part a vaccine contain suspending fluids (liquid which kill or weaken the organism for use in vaccines); sterile water, saline or fluids containing protein; egg proteins (in influenza and yellow fever vaccines); yeast proteins (baker's yeast). Preservatives and stabilizers used include albumin, phenols, glycine, monosodium glutamate (MSG) and 2-phenoxy-ethanol, antibiotics, thiomersal, etc. Inactivating agents such as formaldehyde (to inactivate toxins in influenza virus, poliovirus, and diphtheria and tetanus), β-propiolactone (to inactivate toxins in rabies virus) and glutaraldehyde (to inactivate toxins contained in acellular pertussis vaccines) are also used. Adjuvants enhance vaccine immunogenicity. Adjuvants or enhancers used include aluminum gels or salts (Alum). Alum is used in several licensed vaccines such as diphtheria-pertussis-tetanus (DPT), diphtheria-tetanus (DT), DT combined with Hepatitis B vaccine (HBV), Haemophilus influenza B, IPV, Hepatitis A vaccine (HAV), Streptococcus pneumonia vaccine (SPV), Meningococcal vaccine and Human papilloma virus (HPV).

Do you know?

- ❖ There are four categories of vaccines in clinical trials for Covid19:
- ❖ Whole Virus, Protein Subunit, Viral Vector and Nucleic Acid (RNA and DNA)

Storage of Immunological Products:

The essential storage conditions are always mentioned on the immunological product label. In order to be therapeutically effective, care must be taken while storing Immunological products under the conditions recommended in the product literature. All immunological products are required to be stored below the room temperature. The viral vaccines, such as, smallpox and oral poliomyelitis are more stable at or below their freezing point. Many vaccines need to be stored at 2 – 8 °C in dark and not allowed to freeze. The bacterial vaccines and antitoxins get deteriorated if they are allowed to freeze. These products should be protected from light.

How does a vaccine work?

- ❖ Vaccines reduce risks of getting a disease by working with your body's natural defenses to build protection. Once vaccinated, immune system responds to:
- ❖ Recognize the invading virus or bacteria
- ❖ Produces antibodies to fight disease
- ❖ Remembers the disease and how to fight it.

Quality Control Tests for Immunological Products:

(1) **Increase in virulence tests:** All live vaccines should be tested for virulence. The most commonly used measurement of virulence is the lethal dose required to kill 50% of infected hosts, referred to as the LD_{50}. The LD_{50} measurement allows comparisons across microbes, and the use of host death provides a non-equivocal endpoint.

(2) **Assessing risk to the environment:** The ability of each live vaccine to shed, to spread to contact target and non-target people, and to persist in the environment must be evaluated to provide information for assessing the risk of the vaccine to the environment, taking into account human health.

(3) **Interference tests:** For products with two or more antigenic components, tests are conducted to confirm that there is no interference between individual components, that is, one component causing a decrease in the protective immunological response to another component.

(4) **Consistency of production:** Prior to marketing approval of any new product, each establishment should produce in its facilities three consecutive production batches of completed product to evaluate the consistency of production.

(5) **Stability tests:** Stability studies (based on an acceptable potency test) are performed to establish the validity of the expiry date of the product.

(6) Batch purity test: Purity is determined by testing for a variety of contaminants. Tests to detect contaminants are performed on master seeds, primary cells, MCSs (Master cell stock), ingredients of human origin if not subjected to sterilisation, and each batch of final product prior to release.

(a) Batch safety test: Batches are considered satisfactory if local and systemic reactions to vaccination with the batch to be released are in line with those described in the registration dossier and product literature.

(b) Batch potency test: Batch potency tests are required for each batch prior to release. These are designed to correlate with the host animal vaccination–challenge efficacy studies.

(8) Other tests: Depending on the form of vaccine being produced, certain tests may be indicated. These tests may concern the level of moisture contained in desiccated products, the level of residual inactivate in killed products, the complete inactivation of killed products, pH, the level of preservatives and permitted antibiotics, physical stability of adjuvant, retention of vacuum in desiccated products and a general physical examination of the final vaccine.

REVIEW QUESTIONS

Tablets:

1. Define tablet. What is its importance over other dosage forms?
2. Classify tablets. Write about its advantages and disadvantages.
3. Define following terms giving examples of each:
   (a) Compressed tablet
   (b) Compression coated tablet
   (c) Sugar-coated tablet
   (d) Film-coated tablet
   (e) Enteric-coated tablet
   (f) Gelatin-coated tablets
   (g) Fast dissolving tablets
   (h) Extended-Release Tablets
4. How uncoated tablets are prepared?
5. What is granulation? What is its significance?
6. Name methods of granulation.
7. What is dry and wet granulation?
8. Discuss direct compression method of tablet manufacturing? What are its advantages over other methods?
9. What are coated tablets? What is importance of tablet coating?
10. What are objectives of tablet coating?
11. Enlist types of tablet coating with suitable examples.

12. Explain steps in coating process.
13. Enlist and explain defects in tablet coating.

Capsules:

1. Define capsule. What is its significance over tablets?
2. Classify capsules. Write its advantages and disadvantages.
3. What is hard gelatin capsule? Write about its composition.
4. Discuss stepwise manufacturing of hard gelatin capsule shells.
5. Write about size of hard gelatin capsules.
6. What are various shapes of hard gelatin capsules?
7. Discuss filling methods used in the manufacture of hard gelatin capsules.
8. Discuss stepwise process of filling hard gelatin capsules.
9. Discuss manual hard gelatin capsule filling.
10. What is finishing stage in hard gelatin capsule filling?
11. Enlist defects in hard gelatin capsule.
12. What is soft gelatin capsule? What is its significance over hard gelatin capsules?
13. Describe nature of softgel shell and its contents.
14. Write about size and shapes of softgels.
15. What are base adsorption and minim per gram factor? Why they are determined?
16. Discuss production of softgels. Write about its finishing.
17. How hard and soft gelatin capsules are stored?

Liquid Oral Preparations:

1. What is liquid dosage form? Give examples.
2. What are advantages and disadvantages of oral liquid preparations?
3. Define solution. Classify it giving suitable examples.
4. What are advantages and disadvantages of oral solutions?
5. Discuss any one solution formulation with its method of preparation and use.
6. How solution dosage forms are stored?
7. Define syrup. Classify them with examples.
8. Define medicated, non-medicated and artificial syrups.
9. What are advantages and disadvantages of syrups?
10. Discuss any one syrup formulation with its method of preparation and use.
11. How syrups are stored?

12. Define elixir. Classify them with examples.
13. Define flavoured, medicated and dry elixirs.
14. What are advantages and disadvantages of elixirs?
15. Discuss any one elixir formulation with its method of preparation and use.
16. How elixir dosage forms are stored?
17. Define emulsion. Classify them with examples.
18. What are bases for classification of emulsions?
19. What are advantages and disadvantages of emulsions?
20. Discuss formulation of emulsion with its method of preparation and use.
21. How emulsions are stored?
22. Define oral suspension. Classify them on the basis of therapeutic class.
23. What are flocculated and deflocculated suspensions?
24. What are advantages and disadvantages of oral suspensions?
25. Write about any one oral suspension formulation with its method of preparation and use.
26. How oral suspensions are stored?
27. Define dry powders for reconstitution. Classify them with examples.
28. What are unit dose and multidose powders for reconstitution?
29. What are advantages and disadvantages of dry powders for reconstitution?
30. Discuss any one dry powders formulation for reconstitution with its method of preparation and use.
31. How dry powders for reconstitution are stored?

Topical Preparations:

1. What are topical preparations? Name them.
2. Define ointments. Classify them with suitable examples.
3. What are advantages and disadvantages of ointments?
4. Discuss formulation of anyone ointment with its method of preparation and use.
5. How ointments are stored? Enlist quality control tests for ointments.
6. Define creams. Classify them with suitable examples.
7. What are advantages and disadvantages of creams?
8. Discuss anyone formulation of cream with its method of preparation and use.
9. How creams are stored? Enlist quality control tests for creams.
10. Define pastes. Classify them with suitable examples.

11. What are advantages and disadvantages of pastes?
12. Discuss anyone formulation of paste with its method of preparation and use.
13. How pastes are stored? Enlist quality control tests for pastes.
14. Define topical gel. Classify them with suitable examples.
15. What are advantages and disadvantages of topical gels?
16. What is organogel? Give its example.
17. What is difference between xerogel and hydrogel?
18. Discuss formulation of topical gel with its method of preparation and use.
19. Define liniments. Classify them with suitable examples.
20. What are advantages and disadvantages of liniments?
21. Discuss anyone formulation of liniment with its method of preparation and use.
22. How liniments are stored? Enlist quality control tests for liniments.
23. Define lotions. Classify them with suitable examples.
24. What are advantages and disadvantages of lotions?
25. Discuss anyone formulation of lotion with its method of preparation and use.
26. How lotions are stored? Discuss quality control tests for lotions.
27. What is difference between liniments and lotions?
28. Define: suppositories, pessaries and bougies.
29. Classify suppositories with examples.
30. What are advantages and disadvantages of suppositories?
31. Discuss anyone formulation of suppository with its method of preparation and use.
32. What is difference between suppositories and pessaries?
33. How pessaries are used?
34. How suppositories are stored?

Nasal Preparations:

1. What are nasal preparations? Classify them with examples.
2. What are mechanisms of drug absorption through nasal preparations?
3. List factors affecting systemic bioavailability of drugs through nasal route.
4. Enlist advantages and disadvantages of nasal preparations.
5. Define nasal powders. How nasal powders are prepared?
6. Name drugs delivered in the form of nasal powders.
7. Classify nasal powder delivery devices giving examples.

8. Define insufflators and insufflations. Give examples.
9. Giving example discuss dry powders inhalers.
10. Comment on pressurized metered-dose inhalers.
11. What are advantages and disadvantages of nasal dry powders?
12. Discuss anyone formulation of nasal dry powder with its method of preparation and use.
13. What are recommended storage conditions for nasal dry powders?
14. Why some nasal dry powders are packaged with secondary packaging?
15. What is emitted dose? How it is determined?
16. Enlist quality control tests performed on nasal dry powders.
17. Define nasal gel. What is its significance over nasal dry powders?
18. Classify nasal gels giving examples.
19. Enlist advantages and disadvantages of nasal gels.
20. Discuss anyone nasal gel formulation with method of preparation and use.
21. How nasal gels are stored?
22. Enlist quality control tests applied to nasal gels.
23. What are bioadhesion and mucoadhesion measurement tests performed on nasal gels?
24. Comment on formulation tolerance and isotonicity tests for nasal gels.
25. Explain gelation temperature test and gel strength test.
26. Define nasal spray. Discuss methods of preparing nasal sprays.
27. What is significance of nasal sprays over nasal powders and gels?
28. Classify nasal sprays giving suitable examples of each.
29. What are nasal saline spray and nasal irrigations?
30. Enlist advantages and disadvantages of nasal sprays.
31. Discuss anyone nasal spray formulation with its method of preparation and use.
32. How nasal sprays are stored?
33. Enlist quality control tests applied to nasal sprays.
34. What are spray content uniformity and spray pattern tests applied to nasal sprays?
35. What is pump delivery test for nasal sprays?
36. Define nasal drops. Classify them with suitable examples.
37. What is significance of nasal drops over other nasal preparations?
38. Discuss methods of preparing nasal drops.

39. Enlist advantages and disadvantages of nasal drops.
40. Discuss anyone nasal drop formulation with its method of preparation and use.
41. How nasal drops are stored? Enlist quality control tests applied to nasal drops.

Ear Preparations:

1. What are ear preparations?
2. Write advantages and disadvantages of ear preparations.
3. What is ear drop? What are its types?
4. Discuss anyone ear drop formulation with its method of preparation and use.
5. What is ear irrigation solution? What are its constituents?
6. What are ear ointments and gels? Give examples.
7. What is ear insufflation? What is its use?
8. Give formula and method of preparation of any otic powder for insufflation.
9. How ear preparations are stored?
10. Enlist quality control tests applied to ear preparations.

Powders and Granules:

1. What are powders? Classify those giving examples.
2. What are advantages and disadvantages of powders?
3. What are fundamental and derived properties of powders?
4. How pharmaceutical powders are prepared?
5. Discuss mechanisms involved in size reduction of powders.
6. Define trituration, pulverization and levigation.
7. What is insufflator? What is its use?
8. Describe insufflators giving its examples.
9. What are advantages and disadvantages of insufflator?
10. What are insufflations? Give example.
11. Write about various applications of insufflations.
12. What are dusting powders? Describe them in details.
13. Classify dusting powders giving examples
14. How dusting powders are prepared?
15. Define medical dusting powder, surgical dusting powder and cosmetic dusting powder.
16. What are advantages and disadvantages of dusting powders?
17. How powders are stored?

18. How dusting powders are packaged and applied?
19. What are effervescent powders? Give examples.
20. What is importance and limitations of effervescent powders?
21. How effervescent powders are prepared?
22. Write about eutectic mixture powders giving example.
23. What is granule? What is its significance over powders?
24. Write about ideal properties of granules.
25. Discuss methods of preparing granules.
26. What are effervescent granules? Give examples.
27. Discuss methods of preparing effervescent granules.
28. What are advantages and disadvantages of effervescent granules?
29. Enlist various quality control tests for powders and granules.
30. What is angle of repose and Carr's compressibility index?

Sterile Formulations:

1. Define parenterals? Name them with examples.
2. Classify injectables with examples.
3. What are advantages and limitations of injectables?
4. List out essential requirements of injectables.
5. What is small volume parentral? Discuss its formulation with method of preparation and use.
6. What is large volume parentral? Discuss its formulation with method of preparation and use.
7. What are lyophilized products? What is its significance?
8. Explain how lyophilized products are manufactured?
9. Discuss formulation of lyophilized product with its method of preparation and use.
10. Describe how injectables are stored?
11. What are ophthalmic products? Classify them with examples.
12. Define eye ointment. What are its components?
13. How eye ointments are prepared?
14. Discuss formulation of an eye ointment with its method of preparation and use.
15. What are advantages and limitations of eye ointments?
16. Discuss packaging, storage and applications of eye ointments.
17. What are eye drops? Classify them with examples.

18. Discuss formulation of eye drop with its method of preparation and use.
19. What are advantages and limitations of eye drops?
20. Write about packaging, storage and application of eye drops.
21. Define immunology, immunity and immunization.
22. How infection is spread among people?
23. Define natural, acquired and artificial immunity.
24. What is active and passive immunity?
25. What are humoral and cell mediated immunity?
26. Define immunological products. Classify them with examples.
27. What are sera? Name them.
28. Define antitoxin? What is diphtheria antitoxin? Give its uses.
29. What is tetanus antitoxin? Give its prophylactic and therapeutic uses.
30. What is botulinum antitoxin? Give its indications and mechanism of action.
31. Discuss method of administration and precautions taken during botulinum antitoxin.
32. Write about gas gangrene antitoxin.
33. Define vaccine. What is it made up of?
34. Classify vaccines with examples.
35. What is live attenuated vaccine and inactivated vaccine?
36. What is bacterial vaccine? List its methods of preparation.
37. Discuss vaccine prepared from cultures.
38. Discuss vaccine prepared from killed microorganism.
39. What is viral vaccine? List its methods of preparation.
40. Discuss viral vaccines prepared from free-living animals.
41. Discuss viral vaccines prepared from fertile eggs.
42. Discuss vaccines prepared from tissue culture.
43. Name Covid19 vaccines along with their manufacturers.
44. Discuss about rickettsial vaccine giving its examples.
45. What are toxoids? Name them.
46. What is diphtheria vaccine? How it is prepared?
47. Describe uses of diphtheria vaccine?
48. Write about vaccines that provide protection against diphtheria.
49. How toxins are prepared?

50. Write about toxoid-antitoxin floccules.
51. What is alum precipitated toxoid?
52. Write note on purified toxoid aluminium phosphate.
53. What is tetanus vaccine and staphylococcus toxoid?
54. Discuss formulation of vaccines?
55. Elaborate upon storage of immunological products.

Chapter ...6

PHARMACEUTICAL INDUSTRY AND BASIC CONCEPTS

♦ **LEARNING OBJECTIVES** ♦

After completing the chapter, students will be able to:

- Understand basic structure, layout, sections and activities of pharmaceutical manufacturing plants.
- Define and understand concepts and importance of quality control, quality assurance and cGMP in pharmaceutical industry.
- Understand concepts and importance of calibration and validation in pharmaceutical industry.

6.1 INTRODUCTION

The roots of the pharmaceutical industry, also known as pharmaceutical manufacturing plant, lie back with the apothecaries and pharmacies that offered traditional remedies as far back as the middle ages. Today, it has become an emerging industry worldwide. It is an important element of healthcare systems throughout the world. It comprises of many public and private organizations that discover, develop, manufacture and market pharmaceutical products and devices for human and animal health. The pharmaceutical industry is based primarily upon the scientific R&D of products and devices that prevent or treat diseases and disorders. Many dynamic scientific, social and economic factors affect the pharmaceutical industry. Some pharmaceutical companies operate in both national and multinational markets. Therefore, their activities are subject to legislation, regulation and policies relating to drug development and approval, manufacturing and quality control, marketing and sales.

6.2 PHARMACEUTICAL MANUFACTURING PLANTS

Pharma industry is one of the fastest-growing industries in India. The pharmaceutical industry in the India continues to grow and pharmacists are making an impact on the industry's landscape. Pharmaceutical manufacturing is the process that starts from industrial-scale synthesis of pharmaceutical drugs to manufacturing of their products. The process of pharmaceutical manufacturing can be broken down into a series of unit operations, such as milling, weighing, mixing, granulation, coating, tablet compression, etc.

In addition to unit operations, the process of manufacturing of medicines also includes other aspects that include batch integrity testing, quality assurance, calibration, validation and facility maintenance. The manufacturing plant offers a wide range of dosage forms. The small plants consist of one or two section or units whereas large manufacturing plants consist of many different sections of the dosage forms. The Pharmaceutical manufacturing plant is responsible for producing pharmaceutical products on an industrial scale that follows testing for quality and regulatory approval. Once product is approved for commercialization, its large-scale production begins followed by distribution to sell through various channels.

6.2.1 Basic Structure

A pharmaceutical manufacturing plant is an industry which manufactures and sells pharmaceutical products such as medicines, cosmetics and drugs. The basic requirement of any manufacturing plant is personnel and their functions. Within the working of a pharmaceutical company lies a whole hierarchy of job positions, designations and roles. All the jobs and departments together are responsible for the success and profit of the organization. The organization structure of a "Typical" Pharmaceutical plant is categorized as functional structure, product-oriented structure and matrix structure. Functional organizational structure is present to some extent in most of the major pharmaceutical manufacturing plants. Each function within the plant is organized separately and each function reports to a specific function/department head. Some of the functional departments in a pharmaceutical industry include manufacturing department, sales department, marketing departments, research department and others.

Major advantages of this structure are expertise is concentrated and individuals deal with common issues and interact with others with common skills. The major disadvantages are less communication with groups in other functional areas and fewer people have a thorough understanding of the whole organization. The basic functional structure is presented in Fig. 6.1 whereas a detailed organizational structure is presented in Fig. 6.2. The description of the hierarchical structure followed within a pharmaceuticals industry.

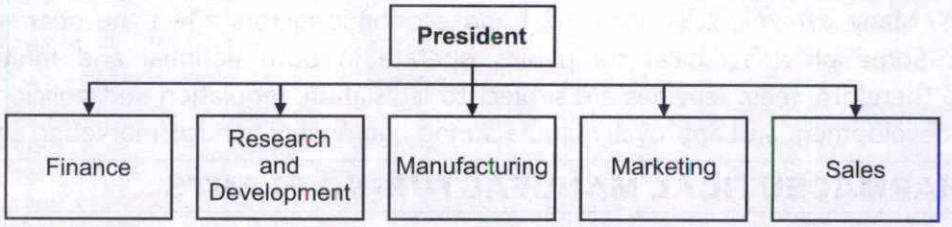


Fig. 6.1: Basic Structure of Pharmaceutical Manufacturing Plant

Senior Most Level Job Positions:

In a pharmaceuticals manufacturing plant, the senior most levels job positions are occupied by administrators, owners, board of directors and other important employees who are responsible for the overall management and operation of the organization. The senior

position people decide and set the goals for the rest of the employees to achieve and are responsible for handling financial issues which is an important part of any industry.

Middle Level Job Positions:

The middle level executives and employees who work under senior level people execute the plans and projects planned and assigned by the senior level employees. They supervise and guide the lower level employees and make sure that the company and its operations run smoothly. The middle level executives hold the most important positions which decide the profit and success results of the company.

Entry Level Job Positions:

The people working at entry level for an authority is concerned don't hold important roles but are a vital part of the industry and are responsible for day to day tasks and functions. The entry level positions are held by those who are not much experienced.

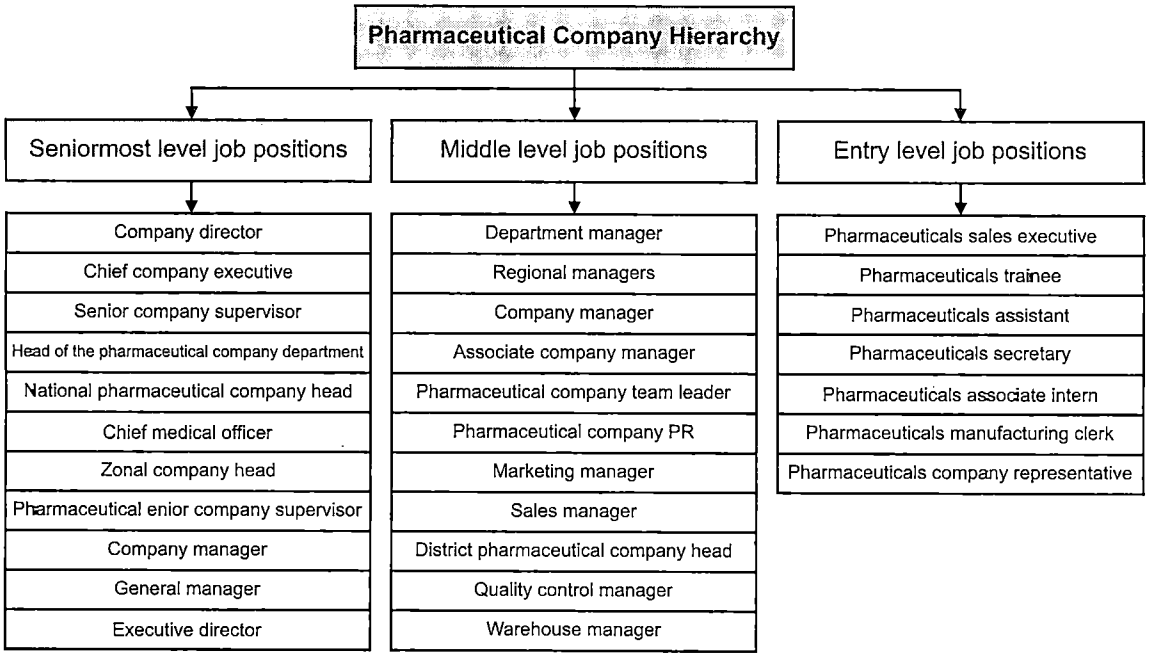


Fig. 6.2: Organizational Structure of Pharmaceutical Manufacturing Plant

6.2.2 Layout

Once decided on where to locate pharmaceutical plant, the next step is to plan a suitable layout because efficiency and performance of good machines and sturdy building depend on the layout of a plant. Plant layout is defined as the method of allocating machines and equipment, various production processes and other necessary service involved in transformation process of a product with the available space of the plant, so as to perform various operations in the most efficient and convenient manner that provides output of high quality and minimum cost. While designing a plant layout, it is important to understand and follow the basic regulatory requirements for the construction of plant building.

According to National Agency for Food and Drug Administration and Control (NAFDAC), layout and design of pharmaceutical manufacturing plant should aim at minimizing the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and any adverse effect on the products. This goal can be achieved by designing the layout in such a way that it follows a logical order corresponding to the steps of the manufacturing operations.

In designing plant layout it is important to understand the manufacturing processes and conduct the facility programming. This is to perform various unit operations involved in the manufacturing of dosage forms in a cost effective manner and with minimum handling in processing the product, starting from the receipt of raw material through the distribution of the finished product for selling. Plant layout must be an integrated design that satisfies the process requirements, personnel flows, material flows, and equipment layout, operational access and maintenance access requirements. The most common pharmaceutical plant layout is presented in Fig. 6.3 showing all necessary arrangements in general.

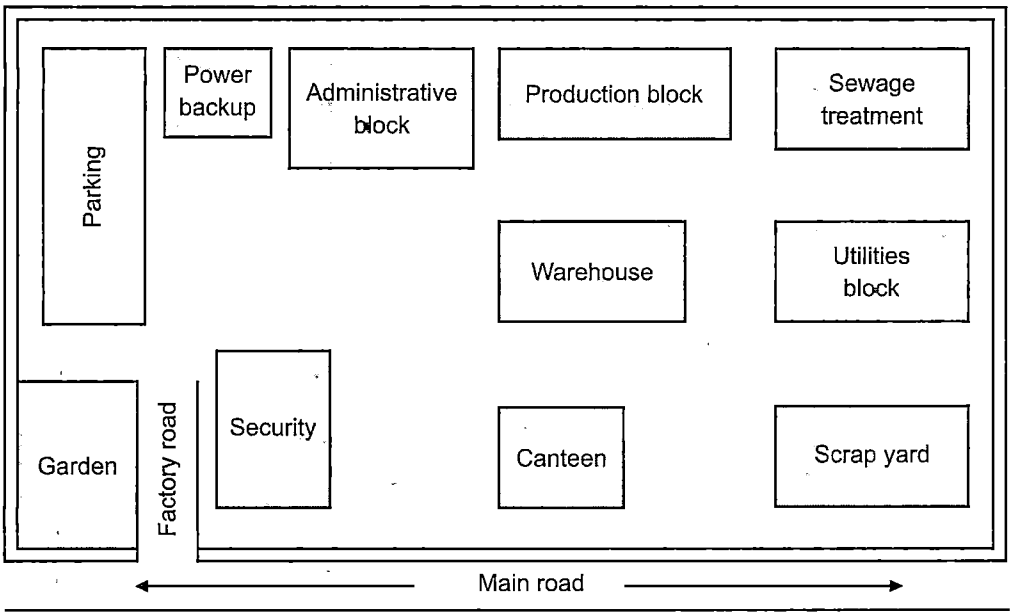


Fig. 6.3: Pharmaceutical Plant Layout

Architectural design must consider proper room finishes, environmental and safety considerations, and must ensure that design is compliant with building codes and fire regulations. Structural framework and building exterior finishes must take into account the interior room environment. That means, use of columns and expansion joints within the cleaner areas of manufacturing facility are minimized wherever possible. Conceptual layout is derived from accommodation schedule and equipment sizing needs. Building blocks of equipment lines are developed and blocks of rooms are assembled based on necessary adjacencies and process requirement.

Planning the layout of a pharmaceutical plant is an important decision as it represents long-term commitment. It is a continuous process as there are always chances of making improvements over the existing arrangement. It should be so designed that the functioning of plant would become very efficient by providing optimum relationship among output, floor area and manufacturing process. A good layout results in comforts, convenience, safety, efficiency, compactness and profits whereas a poor layout results in congestion, waste, frustration and inefficiency. Although pharmaceutical plant layout differs from plant to plant, the basic principles governing pharmaceutical plant layout are more or less same.

(a) Characteristics:

A good pharmaceutical plant layout should possess the following characteristics:

(1) There should be adequate floor space for machines installation and utilization.

(2) Machines should be properly arranged to facilitate minimum material handling necessary for low cost processing.

(3) The layout should facilitate smooth and continuous flow of production process from one point to another to avoid delays.

(4) It must incorporate adequate health, safety and security features, for example, first aid box, fire extinguisher, emergency exit and access points, etc.

(5) The layout should allow effective supervision, coordination and control of the production processes.

(6) There should be room for adjustment and modifications whenever the need arises.

(7) There should be sufficient space for the workers to perform their functions.

(8) The store facility for in-process material should be designed to minimize material handling.

(b) Advantages:

A good layout can provide a number of advantages to workers and management. The advantages of a good pharmaceutical plant layout include but are not limited to:

(1) Easy administration and communication amongst the departments.

(2) Optimum use of available floor space for production operations.

(3) Improved quality of product due to reduced chances of cross contamination.

(4) Efficient arrangement for receipt, transportation, storage, and delivery of raw material and finished goods.

(5) Low cost of material handling and minimized loss due to waste and spoilage.

(6) Conducive working conditions resulting in improved efficiency.

(7) Increased productivity with reduced risk of human error and occupational hazards.

(8) Minimized cost and efforts in supervision, coordination and control over production processes.

6.2.3 Sections

(1) Security Office:

The pharmaceutical plant employs 'Safety Officers' as specified in Factory Act. It is one of the most diverse fields with a board range of potential security vulnerabilities. Facilities protection requires highest level of security services related to access control, ingress and egress monitoring, after-hours protection and alarm monitoring. Security services required for access control, fire prevention and life safety programs, demonstration mitigation, facilities protection, crisis management, emergency or unusual event response, etc. Security guards maintain a book which contains name or in and out time of the person. They are responsible for safety of people working in plant premises.

(2) Garden:

Horticulture is the industry and science of plant cultivation including the process of preparing soil for the planting of seeds, tubers or cutting. In pharmaceutical plants, gardens are maintained surrounding the facility. Trees are planted at proximity of the facility. Clarified water from effluent treatment can be used for watering the gardens.

(3) Vehicle Parking:

Parking is an essential component of the transportation system. Generally, it is located at the periphery of the premises. Separate area provided for parking vehicles of the employee's and the visitors. Separate areas are allocated for parking of 2-wheelers and 4-wheelers. Allotment of parking area depends on industry's size, scope and operations.

(4) Power Backup:

Fuel is required in pharmaceutical industries for generating power during interruption of regular power supply. Generally coal, diesel can be used as an alternative during electrical supply failures whereas canteen requires LPG for cooking. Storage for these resources is located near the generator room. Constant check is kept on the quantity of the material stored and utilized. As these substances are highly inflammable, protection from fire is a basic requirement. Fire safety equipments are placed in vicinity of such facility and people are trained in handling of the same.

(5) Administrative Block:

Administrative block has cabins for Heads of various departments. This block consists of conference rooms and a meeting rooms with different seating capacities. It also comprises library, pantry and crockery storage. In addition, this block also has offices for accounts and finance, general plant administration, and production, planning and control Heads, cabins for production, QA, QC, engineering and maintenance Heads, etc. Other amenities of this block includes rest room, medical services and wash rooms. If building is multistory there are toilets and wash rooms on each floor.

(6) Production Block:

The type of facility in this block depends on budget, how many products are to be made, and what batch sizes are to be produced. Fortunately, while designing the pharmaceutical manufacturing plant, optimal efficiency is achieved through the use of International Building Code (IBC). This allows for future expansion of biggest buildings. Broadly speaking, pharmaceutical production facilities come in three main types:

(a) Single-floor facilities: These are cheapest to build, but ceiling height can impose constraints on materials handling solutions. However, even with small, single-floor buildings, IBCs can be used to achieve full batch transfer from one process to another, that reduce waste product. Creative use of frameworks can enable the use of efficient gravity-fed vertical transfer systems.

(b) Two-floor facilities: These facilities though more expensive to build, can be used to separate materials handling and blending on the top floor, from tableting and packing procedures on the lower floor. This is particularly important for GMP, where isolating potential contaminants and maintaining quality are priorities.

(c) Multiple-floor facilities: These are expensive, but with lots of available space these are highly flexible. However, space can be wasted if due consideration is not given to the plant layout and overall production flow. These facilities provide an opportunity to incorporate new technologies to maximize the efficiency of each production area.

No matter the size or shape of production facility materials handling solutions can increase efficiency, productivity and revenue, if considered early in the design of a pharmaceutical manufacturing plant.

(7) Sewage Treatment:

In pharmaceutical plant most of wastewater is produced by washing equipment at the end of the production process and it depends on the production rate. There are other pollutants includes rejects from reverse osmosis, cleaning of the installations, effluents from laboratories, etc. In order to treat wastewater and purify, every plant sets up sewage water treatment plants.

(8) Utility Service Department:

The utility systems in pharmaceutical plant help to check the quality and safety of their products and ensure they comply with the laws and statutes in the FDA dossier. Utility services include heating, ventilation and air conditioning (HVAC), plumbing, drainage systems, gas systems, sanitation, water, pesticides etc. Other specialized services in a factory include compressed gases, water for pharmaceutical use, vacuum, electricity and room air conditioning. All utilities that could affect product quality are qualified and appropriately monitored and action is taken when these utility limits exceed.

(9) Canteen:

Canteen usually located at the periphery of the industry. Area of canteen depends on the number of workers employed. The canteen furniture will be in accordance to GMP. Food may be provided by company which will lead to maintaining a hygienic cooking facility in

canteen. Employees can have their food in the canteen. Proper safety equipments are to be kept in place. Cooking area has to be maintained under total hygienic condition. People involved in preparation, serving, cleaning of area are to be well trained in each activity like personal hygiene practices, washing of utensils, cleaning of food materials. Sanitation is the general problem associated with canteen facility.

(10) Warehouse:

The warehouse is responsible for all incoming goods including labeling and packaging and for releasing finished products. Once a finished product is received into the warehouse, it does not undergo any further inspections or quality control tests. The warehouse relies upon procedures and well-trained staff to ensure that products arrive safely and with the same quality as when they left manufacturing. It is managed and run in compliance in order for the plant to protect and distribute a quality product. These compliant practices include control over receiving goods, QC, storing materials, components and products, fulfilling picking requests and shipping the product to the marketplace.

(11) Scrap Yard:

During working in the industry, large amount of waste material or scrap is generated. This includes the empty cartons in with raw material or packaging material is plastic sheets, discarded powders, discarded or rejected products, printed packaging materials, machinery/ equipments or parts of machinery/equipments. The most common method employed for destruction of these materials is incineration. All materials moved to the scrap yard are documented systematically; and the record of destruction is maintained. Precaution during incineration process is necessary with respect to the material to be destroyed, fumes generated, toxic gases evolved. If material is to be discarded, then complete procedure for metal processing is used. Security measures taken to prevent thefts of any material stored in scrap yard.

6.2.3 Activities

The pharmaceutical industry comprises of companies involved in the research and development, manufacturing and supply, and commercialization of new therapeutic products working to bring the right treatment to the right patient at the right time.

(1) Research and Development (R&D):

R&D is one of the critical activities in drug development in the pharmaceutical plant. The department is able to research and analyze the products other businesses are creating, as well as the new trends within the industry. It is responsible for creating new medications that physicians use to treat their patients.

(a) Drug discovery: It is the process by which new disease or sickness-fighting compounds are screened and identified. This is the first step in new drug development. During this phase, compounds are identified and tested *in-vitro* and through preclinical testing to demonstrate preliminary for desired efficacy, stability and bioavailability.

(b) Clinical trials: The testing phase of a new drug in human clinical trials is a lengthy and expensive affair. The regulatory authorities demands that potential drug must pass through these trials to demonstrate safety and baseline efficacy. The phase I and Phase II involve only small sample groups of volunteers while the Phase III involves a sample size of thousands of volunteers. Generally, Phase III trials need to demonstrate that a potential drug meets the necessary efficacy requirements with a 95% statistical certainty.

(c) New drug approval: In this activity approval to new drug is obtained from regulatory body to bring a drug to market, upon a successful round of clinical trials. The regulators review rigorous statistical data analysis and test results produced during the clinical trials. Some drugs may be "fast-tracked" if they treat a serious condition that does not currently have many viable treatment options, for example, vaccines to treat Covid-19. After a new drug has been approved, it is taken to large scale manufacturing.

(d) Post-marketing monitoring: Pharmaceutical manufacturers collect data on the efficacy and use of a drug product after it is approved, manufactured and distributed for use. They monitor products for safety, long-term side effects and potential secondary uses for the drug. This activity can identify additional clinical value, such as new methods of delivery, combination of treatments, new uses, patient targeting, etc., for approved drug.

(2) Manufacturing:

The Pharmaceutical manufacturing activity is done to produce drugs on an industrial scale following clinical trials and regulatory approval. In manufacturing, drug substances are converted into dosage-form products. The process of manufacturing pharmaceutical products includes many unique components that include mixing of active drug substances with pharmaceutical excipients, such as binders, fillers, flavouring and bulking agents, preservatives and antioxidants, etc. These excipients may be dried, milled, blended, compressed and granulated to achieve the desired properties before they are manufactured into final solid, liquids and semisolids formulations. In some cases, pharmaceutical manufacturers may produce active pharmaceutical ingredients (APIs), while other manufacturers might purchase APIs in bulk from a third party and prepare them for consumption by adding certain compounds, binders and/or fillers.

(3) Quality Assurance:

In a pharmaceutical manufacturing, quality assurance is involved in several activities such as purchasing, dispatching, warehousing, operational protocols, manufacturing, training, quality control, validation and packaging. Quality assurance involves series of actions which collectively ensure product quality. It establishes specific activities before the start of production which includes the control factors and product evaluation before formation of final product. In pharmaceutical manufacturing, quality assurance ensures that the products are designed and developed in accordance with the requirements of GMP and GLP.

(4) Quality Control:

Quality Control (QC) activity is concerned with sampling, specifications and testing as well as the organization, documentation and release of the product procedures. This ensures the necessary and relevant tests carried out for the release of products. The product to be released for sale or supply should be carried out only after checking their quality. QC is not confined to laboratory operations, but it is involved in all decisions which concern the quality of the product. The QC activity is independent of production.

(5) Warehousing:

Pharmaceutical warehousing activity preserves the integrity of drug products that affect the health and wellbeing of people. It includes proper storage of products to prevent contamination, and to allow for inspection and cleaning of the area. It stores drug products in a manner that must be identified with a distinctive code, for example, the lot's status can be identified as approved, quarantined and rejected. This activity involves designing of written procedures to describe the distribution process, product recalls and appropriate storage conditions for each drug, respectively. Warehousing ensures that the storage of each drug is in line with its specific requirements.

(6) Packaging:

Pharmaceutical packaging operations are performed with a series of integrated machines and repetitive manual tasks. Finished products are packaged in different types of containers such as plastic or glass bottles, foil blister packs, pouches or sachets, tubes and sterile vials. The mechanical equipment fills, caps, labels, cartons and packs the finished products in shipping containers.

(7) Product Education and Compliance:

The product compliance activity involves final licensing of a drug after clinical trials and the subsequent labeling, education and information management related to that product. It ensures that products are labeled in accordance with requirements set forth by the FDA and fact-check marketing/promotional materials that are used to market the drug to physicians and potential patients. In some cases, the product compliance group may audit company operations such as manufacturing, drug testing, etc., to ensure that all operations are in compliance with industry regulations.

(8) Laboratory Activities:

Laboratory operations in the pharmaceutical industry may pose biological, chemical and physical hazards, depending upon the specific agents, operations, and equipment and work practices employed. Lab workers may conduct scientific research to discover drug substances, develop manufacturing processes for bulk chemical and dosage-form products or analyze raw materials, intermediates and finished products. Lab activities are evaluated individually, although Good Lab Practices (GLPs) are applied to many situations.

(9) Cleaning and Maintenance:

Workplace and equipment surfaces may be contaminated by hazardous materials and drug substances during manufacturing and thus requires them to be cleaned. Cleaning activity is performed by washing or wiping liquids and sweeping or vacuuming dusts. Wet mopping and vacuuming is usually used that reduces worker exposures to dusts during cleaning.

(10) Pharmaceutical Distribution:

The distribution activity within the pharmaceuticals industry is responsible for supplying drugs to retail medical shops, hospitals and other healthcare facilities through Supply Chain Management (SCM) to satisfy customer requirements as efficiently as possible. SCM contributes in reducing cost of production and distribution through elimination of waste, compliance with standards and quality, promoting ethical sourcing, curbing unethical practices. In most cases, drug distribution is carried out by third parties that link manufacturers with distributors and retailers including hospital networks.

(11) Patient Assistance Programs:

Patient Assistance Programs (PAPs) are initiatives funded by pharmaceutical manufacturers to distribute free or reduced-rate medicines to people with low to moderate-income or who are underinsured. The eligibility requirements for these programs may vary; some programs demand that the patient be uninsured, while others require that certain income levels are met.

6.3 QUALITY CONTROL

Quality is the degree of excellence a product possesses with respect to its design and conformity with certain prescribed standards and specifications; so as to meet customers' expectations most satisfactorily. Quality control (QC) is an inspection aspect of quality management. Certain observations on the concept of quality can describe it as subjective, relative, conditional or dynamic.

6.3.1 Definition

Quality control can be defined as "part of quality management focused on fulfilling quality requirements." QC can also be defined as "the operational techniques and activities used to fulfill requirements for quality."

ISO 9000 defines quality control as "A part of quality management focused on fulfilling quality requirements". It is the activity concerned with sampling, specification and testing, and documentation and release procedures which ensure that the necessary and relevant tests are performed and the product is released for use only after ascertaining its quality.

6.3.2 Concepts

QC involves establishment of quality standards and installation of systems to ensure that these standards are maintained and practiced. QC analysis regularly checks various quality parameters at each step to produce good quality products. In order to implement an

effective QC program, an organisation first decides which specific standards the product or service must meet. Then, the extent of QC actions is determined, for example, the percentage of units to be tested from each lot. The types of quality control include process control charts, product quality control and process control. The data such as the percentage of units that fail at testing is collected and the results are reported to QC Manager. After this, corrective action is decided and implemented.

(a) Steps in Quality Control:

1. **Establishing quality standards:** In this step quality standards are established in terms of size, design, durability, appearance, etc., on the basis of customers' preferences and cost of production.
2. **Selecting the manufacturing process:** The selection of step in manufacturing process permits output of the required specifications.
3. **Development of measurement techniques:** This step help to ensure whether production conforms to set specifications or not.
4. **Monitoring product quality:** This step of QC designs a system in order to periodically check end products to determine deviations from set quality standards and locates causes of such deviations.
5. **Taking corrective action:** This step is employed to remove causes of deviations.

(b) Significance of Quality Control:

1. **Cost reduction and profit maximization:** QC helps to better utilize productive resources; and eliminate all sorts of wastes. Ultimately it helps to reduce cost and maximize profit for the organisation.
2. **Increase in operational efficiency:** As QC implies control over quality of raw-materials and performance of operators and equipments, etc., it brings about more operational efficiency of the organisation.
3. **Maximum profit and customer satisfaction:** QC minimizes complaints from customers and results in maximum customer satisfaction. Quality help to bring customers back for a repeated purchase that leads to increased sales and consequent increased profit.
4. **Image of the organisation:** QC builds goodwill of the organisation in society. The quality products offered by the organisation establishes an image in the eyes of the public.
5. **Insurance against heavy losses:** QC protects the manufacturer against heavy losses due to rejection of large quantity of sub-standard products.
6. **Promotes employees' productivity:** QC develops a feeling of quality consciousness among employees; that help to promote their productivity.
7. **Morale of employees:** QC increases morale of employees; as they feel that they are working for an enterprise producing goods of superior quality.

(c) Techniques of Quality Control:

1. **Inspection:** Inspection in QC programme is concerned with checking on the performance of items to the specifications set for it. It involves periodic checking and measuring before, during and after the production process. Manufacturing involves several variables, thus inspection is a never ending process.

   (i) Centralized inspection: In this type of inspection, all the work from a department is sent to the Inspection Department, before passing on to the next operation. It ensures impartial supervision; because the inspector is not under the stress of not rejecting the work of a person with whom he has good personal relation. It is easier to keep records of items which are approved or rejected.

   (ii) Floor inspection: In this inspection, inspectors visit the production floor and inspect ongoing operations of the machines, also known as patrolling or travelling inspection. Since work is inspected on the floor, the delay in sending work to next station is avoided. Inspector can immediately locate the fault and suggest rectification. It involves minimum material handling.

2. **Statistical Quality Control (SQC):** SQC is a system for controlling the quality of production within the specified limits by means of a sampling and analysis of inspection results. It determines the extent to which quality goods are being met without necessarily checking every item produced and for indicating whether or not the variations which occur are exceeding tolerance limits. SQC is not to produce a quality product but is merely informing the management about actual status of the operations. It helps to make decision for rejection or acceptance of a particular product. Management takes necessary steps to eliminate the causes of variations, if any, and ensure production of quality products. The techniques of SQC are:

   (i) Process control: The quality characteristics under process control are checked with the help of charts, for example, X-Chart, R-Chart, C-Chart and P-Chart, which help to provide visual aids. These charts are easy to prepare and give early warning of problem. All these charts represent how quality-characteristic is changing from one sample to another. When a plotted point falls outside the control limits (UCL: upper control limit and LCL: lower control limit) a process is said to be out of control and an action to check and correct the process is initiated.

   (ii) Acceptance sampling: Acceptance sampling is used for receipt of materials and dispatch of finished goods. Acceptance sampling plans are best suited when the processes used in manufacturing remain unchanged. The decisions about the quality of batches (accept or reject) are made after inspection of samples. If the sample from the batch of products complies with quality specifications, it is

accepted and vice-versa. There is possibility that a lot of satisfactory quality is rejected on the basis of sample result, called producer's risk. Similarly, the consumer may accept a lot of unsatisfactory quality, called consumer's risk. Acceptance sampling is advantageous when 100% inspection is not possible and useful when inspection may cause damage or complete destruction. It is less expensive than 100% inspection,

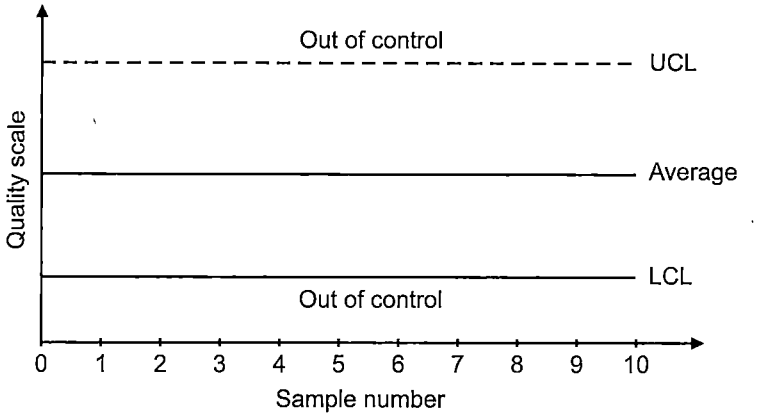


Fig. 6.4: Control Chart

Advantages of SQC:

(1) The costs of inspection are greatly reduced.

(2) Gives an early warning of defects during production operations.

(3) SQC techniques are simple and require no highly skilled operators.

(4) It provides continuous inspection of the product during production.

(5) It enables a process to be held in a state of statistical control.

6.4 QUALITY ASSURANCE

Quality is simply stated as "Fit for use or purpose." It is all about meeting the needs and expectations of customers with respect to functionality, design, reliability, durability, price of the product, etc. Assurance is a positive declaration on a product or service, which gives confidence. Assurance provides a guarantee that the product will work without any problems as per the expectations or requirements. Together quality and assurance as Quality Assurance (QA) focuses on improving the pharmaceutical product and its development process to make it efficient and effective as per the quality standards defined for respective pharmaceutical product.

According to WHO, quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product or service. As a result the term Total Quality Management (TQM) was adopted in most of the industries. With regard to pharmaceuticals, QA can be divided into development, quality control, production, distribution, and inspections.

6.4.1 Definition

QA, also called QA testing, is defined as a procedure to ensure the quality of pharmaceutical products or services provided to the customers by an organization.

ISO 9000 defines QA as "part of quality management focused on providing confidence that quality requirements will be fulfilled".

6.4.2 Concepts

QA is any systematic process of determining whether a product or service meets specified requirements. It helps to give high-quality product that builds trust and loyalty with customers. The standards and procedures defined by a QA program help to prevent product defects before they arise. QA approaches are employed during every stage of a drug's development. The QA process includes reviewing documents, approving equipment, calibration, reviewing training records, reviewing manufacturing records and investigating market returns.

QA process has a defined cycle called PDCA cycle. The phases of this cycle are plan, do, and check and act (PDCA). These steps are repeated to ensure that processes followed in the drug's development and manufacturing are evaluated and improved periodically.

(a) Plan: In this phase, organizations plan and establish the product, process and service-related objectives and determine them to deliver a high-quality end product.

(b) Do: In this phase, product, process and services are developed and tested and necessary changes are made (do).

(c) Check: In this phase, product, process and services are monitored and modified to check whether it meets the predetermined objectives.

(d) Act: In this phase necessary actions implemented to achieve improvements in the product, process and service.

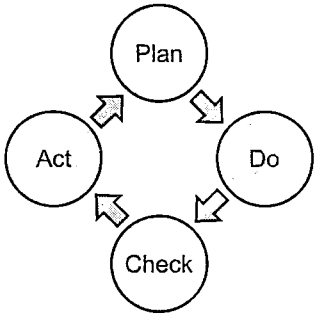


Fig. 6.5: Quality Assurance Process

An organization uses QA to ensure that the product, process and services are designed and implemented with correct procedures. This helps reduce problems and errors, in the final product.

Do you know?

- ❖ The first step of QA is identification of customer needs after which further basic elements of QA are identified.
- ❖ QA depends not only on QC but also on the activities of the entire plant.

(a) Functions of QA:

(1) Technology transfer: Product design document is prepared and trial and error data collected and evaluated. The documents are distributed, checked and approved.

(2) Validation: In validation, validation master plan (VMP) for the entire system is prepared and resource planning for execution is done. Test criteria for approval of validating product and process are set.

(3) Documentation: It controls the distribution and archiving of documents. Any change in a document is made by adopting the proper change control procedure. It also involves approval of all types of documents.

(4) Assuring product quality: It prevents mistakes and defects in manufactured products and avoids problems when delivering process, products or services to customers.

(5) Quality improvement plans: Organizations makes to its stakeholders to improve quality through focused targets and actions.

(b) Quality Assurance Methods:

(1) Failure testing: This method continually tests a product to determine if it breaks or fails. For physical products that need to withstand stress, this could involve testing the product under heat, pressure or vibration.

(2) Statistical process control (SPC): This method is based on objective data and analysis using statistical methods to arrange and control the production.

(3) Total quality management (TQM): This method employs quantitative techniques to continuously make improvements. It depends on facts, data and analysis to support product planning and performance reviews.

Do you know?

- ❖ TQM tools help organizations to identify, analyze and assess qualitative and quantitative data.
- ❖ These tools can identify procedures, ideas, statistics, cause and effect concerns and other issues.

(c) Types of Quality:

(1) Design Quality: Design quality refers to the level of characteristics specified for a product. The characteristics associated with high quality product are high-grade materials, narrow tolerances, special features and high performance. The reliability of a product is considered in the design stage. It is the probability that a product will

perform its intended function, without failure, for a specified length of time. It depends upon the basic design, the quality of materials and the quality of components that go into the final product. To achieve the required reliability, designers need to specify higher priced components. This may lead to higher price but also to higher value for the consumer.

(2) **Conformance Quality:** Once the level of design quality has been determined, the product characteristics are formed into drawings and specifications. The manufacturing people use these drawings and specifications to develop manufacturing specifications and design the operations necessary to produce the product. This includes the floor layout, machinery, test sets, tools and other equipment. A plan for the number of employees required may also be included. The quality person works with the manufacturing person to make the quality system and maintenance of conformance quality an integral part of the manufacturing process.

(d) Quality Systems:

A quality system is a mechanism that co-ordinates and maintains the activities needed to ensure that the characteristics of products, processes or services are within certain limits. A quality system involves every part of an organization that directly or indirectly affects these activities. Typically, the quality system is documented in a quality manual and in the associated documents that specify procedures and standards. There are three basic elements in a quality system:

(1) **Quality management:** Quality management is the means of implementing and carrying out quality policy. Quality management plans goals and manages activities of QC and QA. Quality management personals monitors that all quality goals and objectives are implemented, and corrective actions have been taken.

(2) **Quality control:** QC encompasses all techniques and activities of an organization that continuously monitor and improve the conformance of products, processes or services to specifications. QC also includes the review of processes and specifications and makes recommendations for their improvement.

(3) **Quality assurance:** QA describes all the planned and systematic actions necessary to assure that a product or service will satisfy the specified requirements. Usually this takes the form of an independent final inspection. The QA function represents the customer and is independent of the QC function.

(e) The Quality Audit:

A quality audit is an independent assessment that compares various management activities and quality attributes to a standard. The person performing the quality audit is not associated in any way with the activity being audited. The types of audits include management and quality system audits (Manufacturing, software and service), product specific audits (Manufacturing, software) and activity specific audits (service). Organizations usually use first-party audits to evaluate their own performance. Second-party audits are

conducted by a customer on a supplier. Third party audits are conducted by completely separate companies with no personal stake in the audited organization. Third-party auditors are usually registrars that audit to ISO 9000 series. A customer usually combines a quality system audit with a product-specific audit while third-party audits reviews management and quality system. Quality audits are conducted to assess and ensure that:

(i) Quality plans, methods and procedures are in place.
(ii) Documents are controlled to avoid misuse.
(iii) Standards and regulations are being followed.
(iv) The data system provides accurate and adequate information.
(v) Problems are addressed and corrective actions are taken.
(vi) Products conform to specification requirements.

Audits should be conducted on a scheduled basis. There should be no surprises to the organization being audited. This policy should include all those involved to categorize their workloads and assign personnel to assist in the audit. The audit should not disrupt any ongoing processes or work.

(f) Quality Management System:

Quality is a measure of excellence or a state of being free from defects, deficiencies and significant variations. QC is an essential operation of the pharmaceutical industry. QA is obtaining confidence that, required quality of product or service is satisfactory for their intended use. QA is a wide concept that covers all aspects that collectively or individually impact the quality of the product. Quality management is the act of overseeing all activities and tasks needed to maintain a desired level of excellence. This includes the determination of a quality policy, creating and implementing quality planning and assurance, and QC and quality improvement.

Quality system in the pharmaceutical industry consists of implementing the best Quality Management System (QMS) within the industry. Quality certification is a general term used for certifying the knowledge of individuals and certifying a company's system of quality management. Quality certifications for individuals are available through various organizations such as the American Society for Quality (ASQ). Certifications are granted to show that individuals have demonstrated and maintain knowledge in an aspect of quality management, such as Certified Quality Engineer (CQE), Certified Quality Inspector (CQI), etc.

(c) Quality Assurance Certifications:

The standard ISO 9000: Quality Management Systems (QMS), first established in 1987, helps the organization to ensure quality to their customers and other stakeholders. This certification is issued to company upon on auditing its functions, products, services and processes. The main objective is to review and verify whether the organization follows the process as expected and check whether existing processes need improvement. The latest certification in the ISO 9000 series is ISO 9001:2015. This guidance includes a stronger customer focus, top management practices and improvements to its structure and risk-based decision-making. This certification helps to increase the profit, improves domestic and

international trade, reduce waste and increase the productivity of the employees and provide excellent customer satisfaction.

Do you know?

- ❖ QA Certificate is for those who lead the internal QA process within an organisation and have a responsibility of managing the quality of the assessment processes, practice and the performance of assessors.

(g) Total Quality Management (TQM):

TQM is a management philosophy implemented to all activities through which the needs and expectations of the customer and community, and the objectives of the organization are satisfied in the most efficient and cost effective way by maximizing the potential of all employees in a continuing drive for improvement. TQM is a means of satisfying customers first time, every time; enabling the employees to solve problems and eliminate wastage; style of working, a culture more than a management technique and philosophy of continuous improvement, never ending, only achievable by/or through people. TQM requires that all stakeholders in a business work together to improve processes, products, services and the culture of the company itself. The TQM perspective views quality as the fundamental objective of the organization.

To be successful through implementing TQM, organizations concentrate on the following key elements:

(1) **Focus on the customer:** It is essential to identify the organization's customers. External customers use the organization's product or service. Internal customers are employees who receive the output of other employees.

(2) **Employee involvement:** Since the quality is considered in the work and responsibility of all employees, employees should be involved in quality initiatives. The leader employees have the closest contact with external customers and thus can make the most valuable contribution to quality. Therefore, employees must have the authority to innovate and improve quality.

(3) **Continuous improvement:** The pursuit for quality is a never-ending process in which people continuously work to improve the performance, speed and number of features of the product or service. Continuous improvement means that small, incremental improvement that occurs on a regular basis will eventually add up to huge improvement in quality.

6.5 CURRENT GOOD MANUFACTURING PRACTICE

Good Manufacturing Practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product. The term GMP describes the key requirements for all aspects of pharmaceutical production such as starting materials, premises, equipment,

training and personal hygiene of staff, quality assurance, new product development, pharmaceutical legislation, and product distribution to ensure a consistent product that conforms to all drug safety, quality, and consumer requirements. It involves application of defined principles and practices in industry organization and management. Consumers expect that each product they consume must meet quality standards so that they will be safe and effective.

Detailed written procedures are essential for each process that could affect the quality of the finished product. GMP being a part of QA ensures that products are consistently produced and controlled to the quality standard appropriate to their intended use as per requirements of marketing authorization. GMPs are enforced in the United States by the U.S. FDA, under Title 21 CFR. The regulations use the phrase "current good manufacturing practices" (cGMP) to describe these guidelines. In order to determine compliance, the FDA inspects and makes assessments regarding the manufacturer's ability to manufacture human and animal drugs and equipment being used. The "c" is written in small letters as it is dynamic and it changes. The "c" for "current" is to remind manufacturers that they must employ technologies and systems which are up-to-date in order to comply with the regulation. For these regulations, the practice need not only be "good" but also "current". Current can imply what is generally acceptable in the industry. Therefore, if new standards are introduced which are better than the current, the manufacturer is under obligation to comply with the new procedures, controls, equipment and methodology.

The cGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the cGMP regulations assures the identity, strength, quality, and purity of drug products. This formal system of controls helps to prevent contamination, mix-ups, deviations, failures, and errors. The cGMP inspections are performed in India by state FDA, reporting to the Central Drugs Standard Control Organization (CDSCO). FDA decides whether firms have complied with the cGMPs by inspecting the firm's facilities, carrying out sample analysis and checking the compliance history. Products which do not fulfill the purported purpose or lack of quality control during processing and packaging predispose a firm to regulatory action by the FDA. Therefore, manufacturers need to become aware of the burden of total accountability for obtaining knowledge.

The cGMPs also provide that a person can comply only with the regulations that govern the specific operations they are engaged in. Additionally, these regulations require that a manufacturer not only be compliant but also maintain timely attention of innovations in the industry. New controls must be made effective immediately. Firms have a grand responsibility to ensure adequate education and training is passed onto their employees regarding cGMPs requirements which apply to them. The cGMPs serve as the foundation for assessing whether human pharmaceuticals are safe and effective to use. Additionally, they are the main standard regulations which drug manufacturing firms are expected to adhere. According to cGMP guidelines if any pharmaceutical product passes all specified tests produced in GMP violating manufacturing area that should not be reached in the market.

6.5.1 Definition

The cGMP is defined as the regulations enforced by the FDA that provides for systems to assure proper design, monitoring, and control of manufacturing processes and facilities.

- ❖ The first WHO draft text on GMP was adopted in 1968.
- ❖ GMP in India is prescribed under Schedule M in June, 1988.
- ❖ In India Joint Commissioner (HQ) is authorized by Commissioner of State FDA, to sign and issue the certificates under the WHO-GMP certification.
- ❖ Certification and Membership Fees is ₹ 25,000/- for Indian nationals.

6.5.2 Concepts

Currently, the FDA is the sole national authority mandated and tasked with the responsibility to issue policies on cGMPs. As a rule of thumb, a drug is deemed adulterated if the facilities used to manufacture it and the packaging, and processing do not conform to cGMPs.

(a) The Outline of GMP:

GMP constitutes the license to operate in pharmaceutical manufacturing. GMP guidelines are a series of general principles that must be applied during manufacturing. There are many ways to comply GMP while setting up of pharmaceutical quality system, manufacturing processes and control in an organization. The responsibility to determine the most effective and efficient quality process rests with organization. Following few basic principles are basis of GMP guidelines:

(1) The production and distribution of the drugs must minimize any risk to their quality.

(2) Manufacturing facilities must maintain a clean and hygienic manufacturing area, including laboratories and storage.

(3) Manufacturing facility design, operating principles and environmental conditions must be controlled.

(4) Manufacturing processes must be clearly defined, validated and controlled to ensure consistency and compliance with specifications.

(5) Any changes to the process must be evaluated, qualified or validated as necessary.

(6) Instructions and procedures must be written in clear and unambiguous language.

(7) Operators should be trained to carry out the production and control of products as per approved procedures.

(8) Records should be made during manufacture and quality control. Any deviations are investigated and documented.

(9) The process should remain in a state of control throughout the product lifecycle and improvements must be made when needed.

(10) Records of manufacture and distribution should be retained in a comprehensible and accessible format that can trace the complete history of a batch.

(11) There must be a system in place for recalling any batch from market.

(12) Complaints about marketed products should be examined; the causes of quality defects investigated, and appropriate measures taken with respect to the defective products and to prevent recurrence.

(b) Parts of GMP:

Part I: Good manufacturing practices for premises and materials.

Part IA: Specific requirements for manufacture of sterile parenteral and ophthalmic preparations.

Part IB: Specific requirements for manufacture of oral solid dosage forms.

Part IC: Specific requirements for manufacture of oral liquids.

Part ID: Specific requirements for manufacture of topical products.

Part IE: Specific requirements for manufacture of metered dose inhalers.

Part IF: Specific requirements of premises, plant and materials for manufacture of drugs.

Part II: Requirements of plant and equipment.

(c) Importance of cGMP:

Testing of products alone is not adequate to detect contamination, error, etc., to ensure quality, efficiency and safety. Thus, it is important that drugs must be manufactured under conditions and practices required by the cGMP regulations to assure that quality that can be built into the design and manufacturing process at every step. Facilities that are in good condition, equipment that is properly maintained and calibrated, employees who are qualified and fully trained, and processes that are reliable and reproducible, are a few examples of how cGMP requirements that help to assure the safety and efficacy of drug products. Poor quality drugs can be a disaster for both patients and governments from a health and a cost perspective. Therefore, manufacturers must produce appropriate quality products by following GMP guidelines.

(d) cGMP Regulations:

FDA ensures the quality of drug products by carefully monitoring drug manufacturers' compliance with its cGMP regulations. The cGMP regulations for drugs contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. The regulations make sure that a product is safe for use, and that it has the ingredients and strength it claims on its label. The approval process for new and generic drug marketing applications includes a review of the manufacturer's compliance with the cGMPs. FDA assessors and investigators determine whether the firm has the necessary facilities, equipment, and ability to manufacture the drug it intends to market.

Do you know?

- In India SDCA and CDSCO are the licensing authorities for GMP implementation.
- In India, GMP was made mandatory for all pharmaceutical manufacturing units from 1-7-2005.
- The concept of cGMP was established in 1969 by USFDA in the Code of Federal Regulations (CFR) (21 CFR Part 110).

6.6 INTRODUCTION TO CONCEPT OF CALIBRATION

Calibration means to know how accurate testing and measuring instruments employed in the quality measurement system are. According to ICH calibration can be defined as "The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements". Calibration of instruments and processes is essential for checking their performances against known standards. This provides consistency in readings and reduces errors, thus validating the measurements universally. Calibration is done by comparing instruments against more precise and accurate instrument called master instruments (reference standard). Calibration ensures the measurement accuracy of an instrument compared to a known standard. It also helps to determine the nature and magnitude of an error (if any) of testing measuring instruments. This error is the deviation from the reference standard.

(a) Important Definitions:

(i) Calibration procedure: A documented, verified, and validated process that describes a set of operations in accordance with a given method.

(ii) Calibration provider: Laboratory or facility including personnel that performs calibration in an established location.

(iii) Errors: Result of a measurement minus the true value of the measurand.

(iv) Reference standard: Measurement standard having the highest metrological quality available in an organization.

(v) Uncertainty of measurement: Dispersion of values that can be attributed to the measurand.

Why calibration?

- Calibration brings out the nature and magnitude of an error (if any) of testing measuring instruments.

(b) Calibration Procedure:

The calibration procedure involves comparison of the instrument against primary or secondary standards. Sometimes, it is sufficient to calibrate a device against another device of known accuracy. After the calibration of a device or a process, future operation is

considered to be error bound for a given period of time under similar operational conditions. The process of calibration is carried out in a hierarchical order.

(i) **Highest level:** At this level, primary reference standard is assigned a value by direct comparison with the reference base of SI units. The primary standards are designated and widely acknowledged as having the highest metrological quantities that have values without reference to other standards of the same quantity.

(ii) **Second level:** In this level, the secondary reference standards are calibrated against primary standards of the same quantity using a high precision comparator and making appropriate corrections.

(iii) **Third level:** At this level, working standards are routinely used to calibrate instruments and processes against the secondary reference standards or their representatives.

(c) Calibration Purpose:

(i) If the instrument reads in the same units as the reference standards, the purpose of calibration is to eliminate biases and minimize the instrumental errors.

(ii) If the instrument reads in different units than the reference standards, the calibration serves the purpose of converting the instrument readings to the units of interest.

(d) Advantages of Calibration:

(1) It determines validity of measurements before the calibration.

(2) It assures consistency and compatibility with those made elsewhere.

(3) It helps to test repeatability and reproducibility features of the instruments and processes.

(4) It provides confidence that products meet their specifications and are of desired quality, thus reducing costs and legal liability.

(5) It increases process and product efficiency through correct measurements.

(6) Calibration of devices in the process industry help to assure that the processes are well controlled and that the products meet set specifications.

(7) It generates documentation of performance of instruments and processes to meet ISO 9000, ISO 1400, and QS-9000 standards.

(8) A frequent calibration provides a graphical view of the equipment uncertainty over time as well as reliability of equipment performance.

(9) Measurements made within international standards promotes global acceptance.

(e) Calibration Personnel:

The calibration is conducted by trained and skilled personnel who are essential to the precision of the calibration. Personnel performing equipment calibration is certified to have the qualifications necessary to perform the required calibration. These qualifications are based on training and experience. Calibration personnel may need to have appropriate

clothing (static free clothing, gloves, face masks, etc.) for safety as well as to avoid the possibility of contamination.

Where to get the instruments calibrated?

- One should get all the testing and measuring instruments calibrated at a reputed institute or organization like RRSL, NC QC, Atira, etc.

(f) Calibration services:

All the testing and measuring instruments are calibrated at reputed laboratories which have a set of precise reference standard, instruments and facilities backed up with well-qualified and experienced personnel. These institutes provide good, most accurate and reliable calibration services with due traceability. Some of them provide facilities such as identification of instruments for calibration, at site calibration, single window calibration service, calibration of special instruments and after calibration service. In order to calibrate instruments through outsourcing details such as name and type of the instruments, make, model and the year of manufacturing, operational range with least count and accuracy, relevant standards or calibration procedure (specialized and critical instruments) and general information about customer organization must be provided.

(g) Costs of Calibration:

A successful calibration process requires hardware and software, special equipment, and manpower; hence the costs vary depending on intensity of use of these variables. The cost of calibration depends on what is calibrated and who is calibrating it. In simple cases where a one-off instrument is involved, cost can be lower than one hundred rupees, but complex cases can cost thousands of rupees. Calibration cost depends on whether the calibration is carried out on the premises of calibrating laboratories or on the factory floor being outsourced to third parties.

6.5 INTRODUCTION TO CONCEPT OF VALIDATION

The concept of validation was first introduced by two U.S. FDA officials Ted Byers and Bud Loftus, during 1970's to enhance the standards in order to improve the quality of pharmaceuticals. U.S. FDA informally established and advocated the concept of process validation on 29th Sep. 1978. It was introduced in direct response to several problems in the sterility of large volume parentrals (LVPs). Initially it was applied to validation of LVP manufacturing processes, but latter it was applied to other process such as analytical methods, drug products, computerized systems in clinical trials, labeling or process control, etc. Now validation is an important and integral part of cGMP.

In a guideline, validation is defined as an act of demonstrating and documenting that any procedure, process, and activity can systematically cause the expected results. It includes the qualification of systems and equipment. The prime objective of validation is to manufacture pharmaceutical products of requisite attribute and quality consistently, at the lowest possible cost. Its goal is to confirm that quality is maintained into the system at each step, and not simply tested at the end. Thus, validation is the established documents

evidence which provides a high degree of assurance that a specific method can systematically manufacture a product that meet its preset specification and quality attributes.

(a) Scope of Validation:

Pharmaceutical validation is a vast area of work that practically covers every aspect of pharmaceutical processing activities. Various areas for pharmaceutical validation includes analytical, instrument calibration, process utility services, raw materials, packaging materials, equipment, facilities, manufacturing operations, product design, cleaning operation, etc.

Why equipment is validated?

- ❖ To establish documented evidence
- ❖ To provide high degree assurance
- ❖ For the cost reduction of the product

When equipment is validated?

- ❖ Installation of the new equipment
- ❖ Change of the location of the equipment
- ❖ Modification of the instrument

(b) Planning for Validation:

All validation activities are planned and the key elements of a validation programme are clearly defined and documented in a Validation Master Plan (VMP) or equivalent documents. The VMP is a summary document, which is brief, concise and clear. The VMP contains data on validation policy, organizational structure of validation activities, summary of facilities and systems, equipment and processes to be validated, documentation formats to be used for protocols and reports, planning and scheduling, change control, reference to existing documents, etc.

(c) Validation Team and Its Responsibilities:

A multidisciplinary team of qualified, trained and experienced personnel, in a relevant discipline, is employed to execute validation studies. Its responsibilities are to:

(1) Create, update and review/approve individual project validation plans and validation deliverables.

(2) Ensure validation compliance with the industry's VMP and project validation plan.

(3) Coordinate, implement and verify elements of VMP.

(4) Consult, evaluate and approve changes.

(5) Review and approve IQ/OQ/PQ procedures and plans.

(6) Review test results and makes recommendations regarding release.

(7) Assess risks and develop contingency plan.

(d) The Importance of Validation:

Validation has significance in pharmaceutical industries which includes assurance of quality, process optimization, and reduction of quality cost, minimal batch failures, improved efficiently and productivity, reduction in rejections and increased output. In addition, it is of great value in avoiding capital expenses and reduction of complaints about process failures. It is important in reduced in-process and finished goods testing. It is significant in more rapid and reliable start-up of new equipments, easier scale-up form development work and maintenance of equipment. It helps to improve employee awareness and more rapid automation. It helps to reduce batch to batch variations, achieve reproducible products of same quality, purity and strength, and assure safety and efficacy and to minimize hazardous effects and reduce the chance of product recall from market. Last but not the least it is crucial in terms of government regulation.

(e) Departments and Authorities for Validation:

(i) **Site validation committee:** To develop site master plan.

(ii) **Manufacturing department:** To prepare batches and assist in data collection.

(iii) **QA department:** To approve the process protocol, review and ensure documentation, procedure and reports are in place and compliances.

(iv) **QC department:** To perform testing and generate reports.

(v) **R&D department:** Designing the product and its development.

(vi) **Engineering department:** Installation of equipments, ensure quality and certify plant, facilities, equipment and support systems.

The authorities responsible for validation to execute are Heads of QA, QC and Production, and Validation departments.

What is objective of Validation?

- The objective of validation is to consider appropriate validation characteristics to provide a sound overall knowledge of the capabilities of the analytical method.

(f) Types of Validation:

(1) **Process validation:** It is the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.

(2) **Equipment validation:** It comprises a series of qualifications, such as design, installation, operational, and performance qualification, that provide a high degree of assurance of the consistent, expected functioning of a piece equipment.

(3) **Facilities validation:** It is the documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

(4) **HVAC system validation:** Heating, ventilation, and air conditioning (HVAC) system validation is required for pharmaceutical clean room validation which include air

velocity test, filter leak test, air flow pattern test, non-viable particle count, viable particle count, recovery test, differential pressure monitoring, temperature and relative humidity monitoring noise and light level measurement

(5) **Cleaning validation:** Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure.

(6) **Analytical method validation:** It is the process of documenting and proving that an analytical method provides analytical data acceptable for the intended use.

(7) **Computer system validation (CSV):** CSV, also referred to as software validation, is to prove that the software or system is performing the way it is supposed to work.

(g) Strategies for Validation:

A detailed protocol for performing validation is essential to ensure that the process is adequately validated. Process validation protocols should include the following elements:

1. **Validation master plan:** It provides an overview of the entire validation operation, its organizational structure, its content and planning. Being a summary document, it is brief, concise and clear. VMP bring out all the planned activities with a time frame and clear-cut responsibilities assigned to various people. VMP reflects the organization's highly ordered approach to the validation programme.
2. **Validation report:** Validation report is prepared to assess the adherence to the protocol after manufacturing of batches. It is a written report generated once validation is completed. If validation found acceptable, it is approved and authorized through signature with date. It describes the validation status of the process or equipment and necessary recommendations for routine use.
3. **Expert evaluation:** The validation report of the entire study is evaluated against the protocol requirements by expert authority. It is prepared with conclusions drawn at each stage stated. The final conclusions reflect whether the protocol requirements were met. The evaluation includes an assessment of the planned calibration and maintenance programmes for the equipment and instrumentation to maintain the validated conditions. The evaluation sheet is signed by authorized officers of the organization. The final approval is given by the heads of the validation team and the QC department.

(h) Principles for Validation:

The basic principles for validation may be stated as follows:

1. **Design qualification (DQ):** DQ is the first element of validation of new facilities, systems or equipment. It is a documented verification of the design of equipment and manufacturing facilities. It demonstrates and documents the compliance of the design with GMP.

2. **Installation qualification (IQ):** IQ is an establishment of objective evidence that all key aspects of the process, equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendation of the supplier of the equipment are suitably considered. Installation qualification is performed on new or modified facilities, systems and equipment.
3. **Operational qualification (OQ):** OQ is an establishment of objective evidence about process control limits and action levels which result in product that complies with all predetermined requirements. OQ follows an authorized protocol. The critical operating parameters for the equipment and systems are identified at the OQ stage.
4. **Performance qualification (PQ):** PQ is an establishment of objective evidence that the process under anticipated conditions consistently produces a product which meets all predetermined requirements.
5. **Re-qualification (RQ):** RQ involves minor changes or changes having no direct impact on final or in-process product quality which is handled through the documentation system of the preventive maintenance program.

(i) Process Validation:

Process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products. It is a requirement of cGMP for finished pharmaceuticals as per 21CFR 211 and GMP regulations for medical devices as per 21 CFR 820 and therefore applies to the manufacture of both drug products and medical devices. It involves a series of activities taking place over the lifecycle of the product and process. According to U.S. FDA "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process consistently produces a product meeting its predetermined specifications and quality attributes".

(1) Reason for process validation: The process validation is performed for new product or existing products as per Scale-Up and Post approval Changes (SUPAC) changes. It may be for change in manufacturing site, batch size, equipment, process, composition or components, critical control parameters, vendor of API or critical excipient, specification on input material, respectively. It can also be performed for abnormal trends in product quality parameters through reviews during Annual Product Review (APR) and when there is trend of Out of Specification (OOS) or Out of Trend (OOT) in consecutive batches.

(2) Stages of process validation: Process validation involves a series of activities taking place over the lifecycle of the product and process. These activities relating to validation may be classified as follows:

Stage 1: Process design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2: Process qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.

Stage 3: Continued process verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

(3) Types of process validation:

(i) Prospective validation: It establishes documented evidence prior to process implementation that a system does what it proposed to do based on preplanned protocols.

(ii) Retrospective validation: It is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process.

(iii) Concurrent validation: It is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process.

(iv) Revalidation: It means repeating the original validation effort or any part of it, and includes investigative review of existing performance data.

REVIEW QUESTIONS

1. What is pharmaceutical manufacturing plant? Name manufacturing processes taking place in it.
2. Discuss in detail basic structure of pharmaceutical manufacturing plant.
3. What are different types of pharmaceutical manufacturing plant structure?
4. Name various job positions at different levels in pharmaceutical manufacturing plant.
5. What are job functions of people working at different levels in pharmaceutical manufacturing plant?
6. What is pharmaceutical manufacturing plant layout? What are its characteristics?
7. What are advantages of pharmaceutical manufacturing plant layout?
8. Draw an ideal layout for pharmaceutical manufacturing plant showing its different sections.
9. Enlist various sections in pharmaceutical manufacturing plant.
10. Write about functions of important sections in pharmaceutical manufacturing plant.
11. Name various activities conducted in pharmaceutical manufacturing plant.
12. Discuss about activities of research and development department.
13. Discuss about activities of production department.

14. Define the terms quality and quality control.
15. Describe various steps in quality control.
16. What are producer's risk and customer's risk?
17. Discuss various steps in quality control.
18. Explain significance of quality control.
19. Describe techniques of quality control.
20. What is statistical quality control? What are its advantages?
21. Define quality assurance. What is its significance?
22. What is PDCA cycle in quality assurance?
23. What are functions of quality assurance?
24. Describe methods of quality assurance.
25. What are advantages and importance of quality assurance?
26. What are functions of quality assurance?
27. Describe various methods of quality assurance.
28. Describe types of quality in quality assurance?
29. What is quality system? What are its basic elements?
30. What do you mean by quality audit? What is its significance?
31. What is quality management system? What is its importance?
32. What is quality assurance certification? What is its significance?
33. What is total quality management? What are its key elements?
34. What is GMP? What is its significance?
35. Write about historical background of GMP.
36. Write principles of GMP guidelines.
37. List out parts of GMP.
38. Discuss importance of GMP.
39. Comment on cGMP regulation.
40. What is calibration? What are its objectives and applications?
41. Define the terms: Calibration procedure, Calibration provider, Errors, Reference standard and Uncertainty of measurement.
42. Discuss in detail procedure of calibration.
43. What is purpose of calibration?
44. List out advantages of calibration.
45. Write about calibration personnel and calibration services.

46. What is cost of calibration?
47. Define validation and write about its significance.
48. What is scope of validation?
49. How is validation planned?
50. What is a validation team? Write about its composition and responsibilities.
51. What is importance of validation?
52. Name departments and authorities responsible for validation.
53. Write about various types of validation.
54. What are process validation, equipment validation, facilities validation, HVAC validation and cleaning validation?
55. What is analytical method validation and computer system validation?
56. Discuss strategies for validation.
57. Elaborate upon principles for validation.
58. What is process validation? Write about its reasons.
59. What are stages of process validation?
60. Write about various types of process validation.

Chapter ... 7

NOVEL DRUG DELIVERY SYSTEMS

♦ **LEARNING OBJECTIVES** ♦

After completing the chapter, students will be able to:

- Define and differentiate between conventional drug delivery system and novel drug delivery system.
- Classify and understand the concepts of novel drug delivery systems with examples.
- Understand advantages of novel drug delivery systems.

7.1 INTRODUCTION

Novel drug delivery system (NDDS) is for delivery of drug other than conventional drug delivery system. NDDS refers to the approaches, formulations, technologies, and systems for transporting drugs in the body as needed to safely achieve its desired therapeutic effects. NDDS are carriers which maintain the drug concentration in therapeutic range for longer period of time within the body. It is a combination of advance technique and new dosage forms which are superior to conventional dosage forms. These systems are net result of outcome in search of efficacious treatment of severe diseases.

Advantages of NDDS include optimum dose at the right time and right location, efficient use of expensive drugs and excipients, and reduction in production cost, beneficial to patients, better therapy, improved comfort and standard of living. Basic modes of NDDS are targeted, controlled and modulated drug delivery systems. Factors affecting the design of controlled release products include physicochemical properties of a drug, route of administration, acute / chronic therapy, target sites, the patient and the disease state/level.

What is Novel dug?

- ❖ Novel drugs are often innovative products that serve previously unmet medical needs or otherwise significantly help to advance patient care and public health.
- ❖ The USFDA approved 53 novel drugs in 2020.

7.2 CLASSIFICAION WITH EXAMPLES

(1) Controlled Release Drug Delivery System (CRDDS):

(a) Matrix diffusion type: In these systems the rate of drug release is controlled by diffusion of dissolved drug in the matrix.

(i) **Rigid matrix diffusion:** In this system, drug is dispersed in the insoluble plastic materials like polymers and fatty acids to control its release.

Examples: Zidovudine (Hydroxypropylmethyl cellulose [HPMC]-K4M, Carbopol-934, Ethyl Cellulose [EC]); Metformin HCL (HPMC-K100M, EC); Diclofenac Na (Chitoson, EC, HPMCP, HPMC), etc.

(ii) **Swellable matrix diffusion:** In this system, hydrophilic gums and polyacrilamides are used to control release of highly water soluble drugs.

Examples: Cimetidine hydrochloride, diclofenac sodium, diprophylline, etc.

(iii) **Reservoir system:** In this system, polymer content in coating, thickness of coating and hardness of micro-capsules controls the release of the drug.

Examples: Nico-400 (Niacin; nicotinic acid); Nitro-Bid transdermal (Nitroglycerin).

(b) **Dissolution matrix type:** In this system, the drug is homogeneously dispersed throughout in a rate controlling medium such as waxes like bees wax, carnuba wax, hydrogenated castor oil, which control the drug release by controlling the rate of dissolution.

Examples: Dimetane extencaps (Dextromethorphan), Dimetapp extentabs (Brompheniramine-PPA; Chewable), etc.

(c) **Encapsulation:** In this system, drug release is controlled by dissolution controlling coating excipients like cellulose, polyethylene, glycols, polymethylacrylates, and waxes.

Examples: Ecosprin (aspirin), progesterone tablets, ornade spansules, chlortrimetron repetabs, etc.

(d) **Dissolution and diffusion controlled release system:** In this system, the drug is encapsulated in partially soluble membrane (coat) in which pores are formed that permits entry of aqueous medium into core and drug release starts by diffusion of dissolved drug out of system.

Examples: Aspirin Tablet, Metoprolol Succinate Tablet, Diltiazem Hydrochloride Tablet, etc.

(e) **Osmotic pressure controlled system:** Osmotic drug delivery uses the osmotic pressure of drug or other solutes (osmagents) for controlled delivery of drugs.

Example: Albuterol Tablets, Phenylpropanolamine Tablets, Pseudoephedrine Tablets.

(f) **Chemically controlled system:** These systems depend upon chemical reaction to occur to release the drug from the polymer within which it is contained.

Examples: Zolpidem Tartrate Tablets, Nifedipine Tablets, etc.

(g) **Hydrogel:** These are systems with 3-D structures of hydrophilic polymers having chemical and physical crosslinks which provide an insoluble network structure and desirable protection of liable drugs, proteins and peptides.

Examples: Ciprofloxacin, Diclofenac Na, Ibuprofen, lysozyme, etc.

(h) Ion exchange resins controlled release system: These are the system prepared by embedding the drug molecules in the ion-exchange resin matrix which is then coated with a semi-permeable coating material.

Examples: Nicotine Chewing Gum, ER Diclofenac Na, Isoxsuprine HCl, Diltiazem HCl, etc.

(2) Microencapsulation:

Microencapsulation is a process in which active substances are coated by extremely small capsules.

(a) Microspheres: Microspheres are polymeric micron range spherical particles that can be used as drug carriers wherein the drug can be encapsulated or is in entrapped form.

Examples: Tetanus and Diphtheria Vaccine, Monoclonal antibodies, Gentamicin, Insulin, etc.

(b) Microcapsules: Microcapsules are small spheres with deposition of a thin polymer coating onto small solid particles or liquid droplets, or on dispersions of solids in liquids.

Examples: Potassium Chloride, Acetaminophen, Vitamin A Palmitate, Progesterone.

(c) Microparticles: Microparticles are spherical particles of 1–1000 μm size that serve as multiunit drug delivery systems with well-defined physiological and pharmacokinetic benefits in order to improve the effectiveness, tolerability, and patient compliance.

Examples: Sulfasalazine Tablet, Mesalamine Tablet, Olsalazine Capsule, Balsalazide Tablet.

(3) Mucoadhesive Drug Delivery System (MDDS):

Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended period of time by interfacial forces. In pharmaceutical sciences, when the adhesive attachment is to mucous or a mucous membrane, the phenomenon is referred to as mucoadhesion. Mucoadhesive drug delivery systems can be classified as:

(a) Oral delivery system: Oral mucosal drug delivery system is for administration of drug for immediate and controlled release action by preventing first pass metabolism and enzymatic degradation due to GI microbial flora providing local and systemic action.

(i) Buccal delivery system: Buccal drug delivery system is for administration of the desired drug through the buccal mucosal membrane lining of the oral cavity.

Examples: Metronidazole Tablet, Morphine Sulphate Tablet, Nifedipine Tablet, Omeprazole Tablet, Oxytocin Tablet, etc.

(ii) Sublingual delivery system: It is the delivery system of drugs which is placed below or under the tongue and allowed to dissolve.

Examples: Lorazepam Tablet, Zolpidem Tablet, Sufentanil Tablet, Nystatin Tablet, etc.

(b) Vaginal delivery system: It is a drug delivery system in which drugs are administered through vagina using dosage forms like creams, tablets, foams, gels, ointments, suppositories and bogies.

Examples: Clotrimazole Cream, Progesterone (Prochieve®) Ointment, Nonoxynol-9 (Gynol II®), etc.

(c) Rectal delivery system: It is a drug delivery system for administration of drug through rectum by creams, gels, ointments, suppositories, solutions and suspensions.

Examples: Ramosetron Tablet, Quinine Gel, Zinc Oxide Ointment, Theophylline Film, etc.

(e) Nasal delivery system: It is a drug delivery system for administration of drug through nose by creams, gels, ointments, solutions, suspensions and bogies.

Examples: Leuprolide Nasal Spray (Synarel®), Apomorphine, Mometasone Furoate Nasal Spray (Metaspray®), Xylometazoline HCl (Parwin®), etc.

(f) Occular delivery system: It is a drug delivery system for administration of drug through eye by gels, ointments, solutions and suspensions.

Examples: Fluorescein Isothiocyanate Ophthalmic Strip, Amphotericin B Eye Drop, Riboflavin Eye Drop, Metronidazole Ophthalmic Ointment, Miconazole Eye Drop, Cyclosporine A Eye Drop, etc.

(4) Implantable Drug Delivery System (IDDS):

These are the drug delivery systems to provide extended release (ER) of a drug for the desired duration, fabricated by using non-degradable and biodegradable polymers to release drugs to the bloodstream, continuously.

(a) Implants: An implant is a medical device manufactured to replace a missing biological structure, support a damaged biological structure, or enhance an existing biological structure. It is a drug delivery system that allows targeted and localized drug delivery to achieve a therapeutic effect with lower concentrations of drug.

Examples: Histrelin (Vantas®), Levonorgestrel (Jadelle®), Etonogestrel (Implanon®), etc.

(a) Osmotic pump: The osmotic pump is a reservoir system that contains an osmotic agent that acts to imbibe water from the surrounding medium via a semipermeable membrane which is permeable to water but impermeable to drug.

Examples: Albuterol (Volmax®), Phenylpropanolamine (Acutrim®), Chlorpheniramine (Efidac 24®), Verapamil HCl (Covera HS®), etc.

(5) Transdermal Drug Delivery System (TDDS):

TDDS releases drug at a zero order rate and is an ideal system for maintaining constant drug levels. In order to achieve optimal drug therapy and to reduce side effects, many types

of transdermal system have been developed till date. TDDS are defined as self contained, discrete dosage forms applied to the intact skin, usually patches, to deliver the drug through the skin at a controlled rate by diffusion, for local and systemic effects.

(a) Sonophoresis: It is a drug delivery method where ultrasound is used to increase the absorption of topical compounds into the epidermis, dermis and skin appendages.

Examples: Diclofenac Na Gel, Insulin Solution, Lidocaine Solution, etc.

(b) Membrane permeation controlled TDDS: In this system, the drug reservoir is sandwiched between drug impermeable membrane and rate controlling membrane.

Examples: Nitroglycerine, Scopolamine, Transderm-Nitro, Transderm-Scop, Catapress, Estraderm, etc.

(c) Adhesive dispersion TDDS: In this system, the drug reservoir is prepared by directly dispersing the drug in an adhesive polymer.

Examples: Nicotine, Fentanyl (Duragesic®), Buprenorphine (BuTrans®), Estrogen (Evra), Clonidine, Nitroglycerin, Verapamil, etc.

(d) Polymer matrix diffusion controlled TDDS: In this system, the drug reservoir is prepared by dispersing the drug homogenously in a hydrophilic and lipophilic polymeric matrix.

Examples: Nitroglycerine (Nitro Dur®), Atenolol Transdermal Gel, etc.

(e) Microreservior type TDDS: It is a combination of reservoir and matrix diffusion type TDDS. This type of drug delivery system offers wide scope in controlling rate of drug delivery.

Examples: Norgestomet, Nitroglycerine, Oestradiol, Clonidine, Nicotine and Testosterone transdermal patches.

(6) Gastroretentive Drug Delivery Systems (GRDDS):

GRDDS are dosage forms that can be hold within the stomach which has ability to prolong gastric residence time (GRT) and control release of a drug thereby increases drug concentration to improve bioavailability.

(a) Floating systems: Floating drug delivery systems (hydrodynamically controlled systems) are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.

Examples: Famotidine Tablet, Venlafaxine HCl Tablet, Ciprofloxacin HCl Tablet, 5-Fluorouracil Tablet, Diclofenac Na Tablet, Prednesolone Tablet, Cinnarizine Tablet, etc.

(b) Low-density systems: Low density GRDDS, also called microballoon, is a microsphere multiple unit systems with a characteristic internal hollow structure made of low-density materials (< 1 g/cm^3) showing an excellent *in-vitro* floatability in the stomach.

Examples: Ranitidine Hydrochloride Tablet, Propranolol Hydrochloride Tablet, Loratadine Tablet, Diltiazem HCl Tablet, etc.

(c) High density systems: These high density GRDDS have a density of ~3 g/cm^3, retained in the rugae of the stomach and are capable of withstanding to its peristaltic movements.

Examples: Clopidogrel bisulfate Tablet, Propafenone HCl Tablet, Atenolol Tablet, etc.

(d) Inflatable systems: This system consists of osmotically controlled drug delivery device and an inflatable support in a biodegradable capsule that when reaches to stomach, inflatable capsule disintegrates to release the drug.

Examples: Glipizide Tablet, Clarithromycin Tablet, Ciprofloxacin Tablet, etc.

(e) Gastro-adhesive systems: These are the GRDDS which bind to the gastric epithelial cell surface or mucin, and prolong the GRT by increasing the closeness and duration of contact between the dosage form and the biological membrane.

Examples: Chlorothiazide Tablet, Moxifloxacin HCl Tablet, Acyclovir Tablet, Nizatidine Tablet, Gliclazide Tablet, etc.

(f) Superporous hydrogels: Superporous hydrogel GRDDS is a composite polymer matrix made of a solid hydrogel and air which upon oral administration instantly swell in the stomach up on water absorption through open porous structure by capillary force and maintain its integrity in the gastric fluid to release the drug.

Examples: Rosiglitazone Maleate Hydrogels, Rabeprazole Sodium Hydrogels, Vildagliptin Hydrogels, Rosiglitazone Maleate Hydrogels, etc.

What is the fastest mode of delivery for drugs?

- Intravenous (IV) drug delivery in which the drug is injected directly into a vein and enters the bloodstream is the fastest mode of drug delivery.

(7) Nasopulmonary drug delivery system (NPDDS):

NPDDS is a system in which drugs are insufflated through the nose. It involves inhalation of drug formulation through mouth and the further deposition of inhaled drugs in lower respiratory airways.

(a) Inhalers: Dry powder inhaler (DPI) is an effective, efficient and environmentally friendly way of delivering drug breathed through the mouth and into the lungs.

Examples: Indacaterol/Glycopyrronium Inhaler, Beclomethasone Dipropionate Inhaler, Insulin Inhaler, Fluticasone Furoate Inhaler, etc.

(b) Nasal sprays: Nasal sprays are systems to deliver liquid formulation to a limited area in the anterior part of the nasal cavity for local or systemic effects.

Examples: Epinephrine Spray, Methoxamine Spray, Serotonin Spray, Vasopressin Spray, Cocaine Spray, etc.

(c) Nebulizers: A nebulizer is a medical device that turns liquid medicine into a very fine mist that a person can inhale through a face mask or mouthpiece that directly and quickly reach to the lungs.

Examples: Albuterol sulphate (Accuneb®) Nebulizer, Levalbuterol HCl (Xopenex®) Nebulizer, Aztreonam (Cayston®) Nebulizer, Tobramycin (Bethkis®) Nebulizer, etc.

(d) Metered Dose Inhaler (MDI): MDI is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized drugs, wherein a medication is mixed in a canister with a propellant and the preformed mixture is expelled in exact measured amounts upon actuation of the device, that is usually self-administered by the patient via inhalation.

Examples: Salmeterol (Serovent®), Albuterol Sulfate (Ventoline®), Beclomethasone Dipropionate (Qvar®) and Fluticasone Propionate (Fluvent HFA®) MDIs, etc.

(8) Targeted Drug Delivery:

Targeted drug delivery, also called smart drug delivery, is a method of delivering medication to a patient in a manner that increases the concentration of the drug in some parts of the body relative to others.

(a) Liposomes: Liposomes are small artificial vesicles of spherical shape prepared from cholesterol and natural non-toxic phospholipids.

Examples: Enoxacin, Amphotericin B, Minoxidil, Cytosine Arabinose, DNA, RNA, Antisense Olgionucleotides, Ribozymes, etc.

(b) Microparticles: Microparticles are solid biodegradable microspheres bearing a drug dispensed or dissolved throughout particles matrix having potential in controlled-release of drugs.

Examples: Tetanus and Diphtheria Vaccine, Monoclonal Antibodies, Glipizide, Leuprorelin Acetate, Triptoreline, etc.

(c) Niosomes: Niosomes are stable non-ionic surfactant-based bilayer vesicles formed mostly by non-ionic surfactant and cholesterol.

Examples: Nimesulide, Flurbiprofen, Piroxicam, Ketoconazole, Bleomycin, etc.

(d) Nanoparticles: Nanoparticles are amorphous or crystalline solid nanospheres and nanocapsules (size 10-200 nm) that adsorb and/or encapsulate a drug, thus protecting it against chemical and enzymatic degradation.

(i) Nanotubes: Nanotubes are hallow-tubes made of 2-D hexagonal lattice of carbon atoms with diameter in nanometers that have high surface modification ability used as carrier, which can be filled and sealed, for potential drug delivery.

Examples: Cisplatin, Doxorubicin, Recombined Proteins, Antibodies, Genes, Gemcitabine, Paclitaxel, Acetylcholine etc.

(ii) **Nanowire:** Nanowire is a delicate, very small system loaded with drug and specifically targeted to the site to reduce side effects and increase therapeutic effects.

Examples: Levodopa, Doxorubicin, Carmustine, Cetuximab, Cytarabine, Daunomycin, Docetaxel, Epirubicin, 5-Fluorouracil, etc.

(iii) **Nanocantilever:** Nanocantilever is a simplest micro-electro-mechanical system (MEMS) coated with antibodies, providing a detector capable of sensing the presence of single molecules of clinical importance.

Examples: Hyaluronic acid, clinical diagnosis, drug screening, pathogen detection.

(iv) **Nanoshells:** Nanoshells are hollow silica spheres covered with gold to which antibodies are attached enabling the shells to target certain cells.

Examples: Paclitaxel (PTX), Curcumin, Doxorubicin, etc.

(v) **Quantum dots:** Quantum dots are fluorescent semiconducting inorganic nanocarriers used in drug delivery and cellular imaging.

Examples: siRNA, HSV-TK/GCV gene, Paclitaxel, Doxorubicin, Buprenorphine, etc.

(vi) **Nano pores:** Nano pores are holes that are so tiny that DNA molecules can pass through them one strand at a time used for highly precise and efficient DNA sequencing and to control rate of drug's diffusion in body.

Examples: DNA, Pancreatic β-cells, Catalase, Endostatin, Vitamin C, etc.

(vii) **Gold nanoparticles:** Gold nanoparticles are solid core of a gold atom surrounded by negative reactive groups on the surface that can be functionalized by adding a monolayer of surface moieties used for drug delivery.

Examples: Aurimune (CYT-6091), Curcumin, Camptothecin, Tumor Necrosis Factor-α, Mercaptopurine, Folic Acid, etc.

(e) **Monoclonal antibodies:** Monoclonal antibodies are identical immunoglobulins generated from a single β-cell clone which recognize binding sites and bind to single antigen in damaged cells that has applications as therapeutic and targeting agents.

Examples: Abciximab, Adalimumab, Alefacept, Alemtuzumab, Basiliximab, Belimumab, Bezlotoxumab, Canakinumab, etc.

(f) **Resealed erythrocytes:** Resealed erythrocytes are biocompatible and biodegradable carriers that possess very long circulation half lives and can be loaded with a variety of chemically and biologically active compounds prepared using chemical and physical methods used for the delivery of drugs.

Examples: Amphotericin B, Danorubicin, Morphine, Doxorubicin, etc.

Do you know?

- The science of controlled release was originated from the development of oral sustained release products in the 1940s and early 1950s.

(9) Ocular Drug Delivery Systems (ODDS):

ODDS are dosage forms, vehicles, or systems intended for instilling, administering, or delivering drug/medicine to eye.

(a) Ocusert: Ocusert is a flat, flexible, elliptical drug delivery system designed to be placed in the inferior cul-de-sac between the sclera and eyelid to release the drug at predetermined and predictable rates eliminating the frequent administration of the drug.

Example: Pilocarpine ocusert (Pilo-20 and Pilo-40).

(b) Artificial tear insert (ATI): ATI is a sterile, rod shaped device made of silicone elastomer for sustained release of drug.

Examples: Lacrisert (Tetracycline), Succinylated Collagen.

(c) Contact lens: Contact lenses are thin circular lenses saturated with drug and placed directly on the surface of the eyes to release drug from these lenses over long period of time.

Examples: Fluorescein, Pilocarpine, Chloramphenicol and Tetracycline, Prednisolone Sodium Phosphate, etc.

(d) Ocular Iontophoresis: Ocular iontophoresis is a non-invasive and safe physical method to deliver drugs, including medicine ions and charged macromolecules into anterior and posterior segments of the eye that penetrates poorly permeable ocular tissues, such as the corneal epidermis.

Examples: Dexamethasone Phosphate, Oligonucleotides, 6-Hydroxydopamine, Zinc Salts, Iodide, Methylprednisolone Hemisuccinate, etc.

(e) Collagen shield: Collagen shield is a biocompatible and safe multipurpose ophthalmic lens made of a natural protein with weak antigenicity, hydrated before the insertion into the eye in which the drug is loaded into the drug solution for a period of time prior to application.

Examples: Gentamycin and Dexamethasone.

(10) Intrauterine Drug Delivery System (IUD):

An IUD is a small piece of plastic that is inserted through the cervix and placed by a clinician into the uterus to prevent pregnancy.

(a) Medicated intra uterine device: It is a device capable of delivering drugs to uterus.

Examples: Copper bearing IUDs (Tcu380A and MLCu-375; made of plastic with copper sleeves and/or copper wire on the plastic) and Progesterone IUDs (LNG-20 and Progestasert), etc.

(b) Non-medicated IUD: Non-medicated IUD exerts its contraceptive action by producing a sterile anti-inflammatory response in the endometrium by its mechanical interaction.

Examples: Stainless steel IUDs, Lippes loop, Dalkon shield, Saf-T-coil, etc.

(11) Vaginal Drug Delivery System (VDDS):

VDDS is an effective means for achieving a continuous delivery of drugs systemically as well as locally.

(a) Vaginal ring: Vaginal ring is a circular ring type drug delivery device designed to release the drug in a controlled fashion after insertion into the vagina.

Examples: Dapivurine, Etonogestrel + Ethinyl estradiol (NuvaRing®), Estradiol (Estring®), etc.

(b) Vaginal tablet: It is a tablet dosage form inserted into the vagina to treat infection.

Examples: Itraconazole, Clotrimazole, Metronidazole, Prostaglandins, etc.

(c) Vaginal suppository: Vaginal suppository is a solid medication that is inserted into the vagina with a special applicator.

Examples: Miconazole Nitrate, Prostaglandin E2, etc.

(d) Vaginal creams: It is cream used for treating vaginal infections, applied with a special applicator.

Examples: Dehydroepiandrosterone Sulphate, Miconazole Nitrate, Progesterone (Prochieve®), Nonoxynol-9, Clotrimazole (Trivagizole®), Clomazol®, Canestan®, etc.

(e) Vaginal gels: It is a gel composed of active and/or inert ingredient(s), intended for administration in or around the vagina.

Examples: Oxybutynin, Liposomes, Nonoxynol-9, etc.

(f) Vaginal ointment: It is an ointment for treating vaginal infections, applied with a special applicator.

Examples: Tioconazole (Vagistat-1®), Candicidin, etc.

(g) Vaginal pessaries: A vaginal pessary is a removable device placed into the vagina with a special applicator and is made up of compressed and molded tablets designed to support areas of pelvic organ prolapse.

Examples: Canestan®.

Do you know?

- Sugar and enteric coating of pills and tablets was reported in the late 1800s.
- Enteric coating of tablets and incorporation of second drug to sugar coating layer was reported in 1938.
- First sustained release product was marketed in 1952.

7.3 ADVANTGAES OF NDDS

1. NDDS are safe with high efficacy exhibiting improved pharmacokinetics and decreased dosing frequency.
2. Reduction in the total amount of drug administered over the period of treatment.

3. These systems improve the therapy by increasing the duration of action and reducing the side effects.
4. It increases the patient compliance and provides convenient route of administration.
5. It helps to achieve targeting of drugs to specific sites with reduced side effects.
6. It offers reduced blood level fluctuation characteristic of multiple dosing.
7. Reduction in the incidence and severity of both local and systemic side effects.
8. It provides protection from the first pass metabolism and gastro intestinal tract degradation thus maximizing availability with minimum dose.
9. Drug targeting towards the tissue or organ reduces toxicity to the normal tissues showing improved patient compliance.
10. Lower healthcare costs to both short and long term hospitalization and workable treatments for previously incurable diseases.

7.4 CHALLENGES OF NDDS

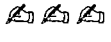
Drug delivery systems suffer from major challenges of delivering poorly soluble drugs and bioavailability hurdles. NDDS development process has monetary, regulatory and patenting challenges associated with research in India. It demands high capital investment and is time consuming, expensive and faces the problem of toxicity, low efficacy, biocompatibility, side effects, fast excretion and degradability. Although it has claimed for reduction of unwanted side effects of drugs, to date very limited clinical data is available to actually support these claims. The lack of specific methodologies for testing effects of NDDS in body remains questionable and establishing safety profile of NDDS based product is challenge for regulatory approval of product. Additionally, there are no specific regulatory guidelines for NDDS products and thus pharmaceutical companies, to obtain market approval of product, have to convince regulatory authority based on scientific concepts. Moreover, DCGI has approved several NDDS products without appropriate clinical testing and strong scientific base, which dilutes the research in NDDS field.

The lack of standard protocols for NDDS characterization at physico-chemical and biological levels has often limited the research efforts to determine the toxic potential of NDDS products in the early stages of testing, which has resulted in the failures during late-phase clinical trials. To simplify and/or shorten the approval process for NDDS products a closer cooperation among regulatory agencies is warranted. Further, patent defending for NDDS is difficult, because there are already existing patents of some NDDS. The other patent issues include patent land grab and overlapping patents. There is lack of discussion platforms, for scientists to learn from failures in NDDS research, and coordination amongst academia, industries, physician, patients and economist for data gathering about performance of marketed NDDS. These challenges can be addressed by development of specific regulatory guidelines, devising specific methodologies to evaluate NDDS and by promoting multidisciplinary research to resolve associated safety issue.

Despite these challenges, positive regulators, low cost scientific man power, significantly low production cost, low cost of clinical trials has boosted R&D in NDDS in Indian pharmaceutical firms. Indian government has also initiated setting up of Drug Development Promotion Foundation (DDPF) and a Pharmaceutical R&D Support Fund (PRDSF) for promoting research in development of NDDS. Many pharmaceutical firms have entered into collaborative research with academic institutes and with foreign companies which has allowed innovation in the field.

REVIEW QUESTIONS

1. What is novel drug delivery system?
2. What are advantages of novel drug delivery systems?
3. Name factors affecting the design of controlled release products.
4. Classify novel drug delivery systems with examples.
5. What are controlled drug delivery systems? Classify them with examples.
6. Classify microencapsulation drug delivery systems giving examples of each.
7. What are mucoadhesive drug delivery systems? Classify them with examples.
8. What is implantable Drug Delivery Systems? Classify them with examples.
9. What is transdermal drug delivery system? Classify them with examples.
10. What are gastroretentive drug delivery systems? Classify them with examples.
11. What are nasopulmonary drug delivery systems? Classify them with examples.
12. What is targeted drug delivery system? Classify them with examples.
13. What is ocular drug delivery system? Classify them with examples.
14. What is intrauterine drug delivery system? Classify them with examples.



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Dr. ASHOK HAJARE has completed his B. Pharm., M. Pharm. and Ph.D. (Pharm. Sci.) from Bharati Vidyapeeth Poona College of Pharmacy, Pune. He has 28 years of UG, PG and Ph. D. teaching and research experience. He taught almost all the subjects belonging to Pharmaceutics. Currently, he is working as Professor and Head Dept. of Pharmaceutical Technology at Bharati Vidyapeeth College of Pharmacy, Kolhapur. He is guiding 8 Ph.D. students (one awarded degree) and guided more than 50 students at the Masters' level. He has authored EIGHTEEN books and has more than 80 research papers and review articles published in national and international journals of repute with very good citations and h-index to his credit. He has presented many research papers in various national and international conferences and symposiums organized by AICTE, PCI, APTI and IPA. He has filled 05 patents at Indian Patent Office Mumbai. Dr. Hajare is a life member of APTI India, International Society for Lyophilization-Freeze Drying Inc., USA and Professional Member of Association of Pharmaceutical Research Chennai. He has been awarded 'Barr. P. G. Patil Ideal Teacher Award' conferred by Shivaji University, Kolhapur in 2014, 'Best Teacher Award' by Rotary Club of Kolhapur 2015 and 'Best Teachers Award' by Avishkar Foundation 2017 at Goa for his outstanding contribution in the field of Pharmacy Profession especially Education. He has been a resource person for 'Pharmacist Refresher Course' conducted by MSPC, Mumbai and delivered many lectures at various national and international conferences, symposium, workshops and faculty development programmes.

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